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SEARCH REQUEST FORM

09/10/99

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Serial Number: 09/314,606 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention ANTIVIRAL PHOSPHONOMETHOXY NUCLEOTIDE ANALOGS HAVING INCREASED ORAL BIOAVAILA

Inventors (please provide full names): ARIMILLI ET AL

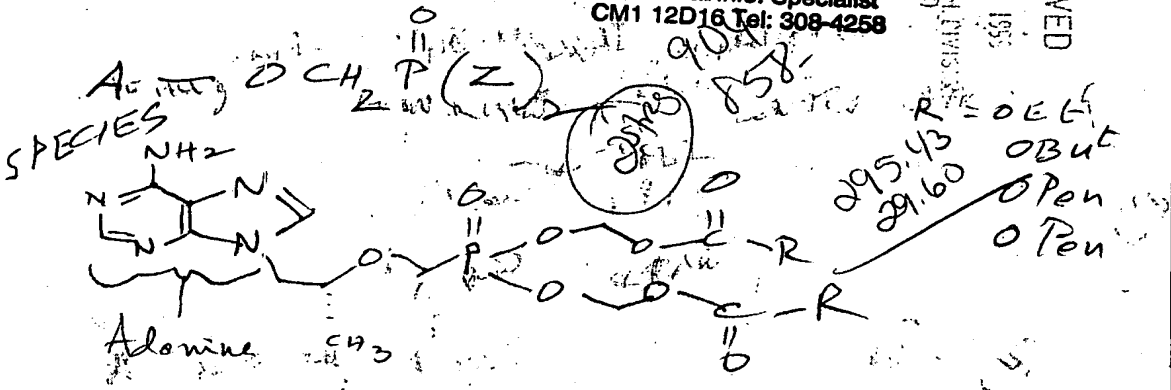
Earliest Priority Date:

Keywords (include any known synonyms registry numbers, explanation of initialisms):

ANTIVIRAL
THIOPHONOMETHOXY NUCLEOTIDE ANALOGS
ORAL BIOAVAILABILITY,
METHOD COMPRISING CONTACTING A CELL

Search Topic:
Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadest or most relevant claim(s).

Point of Contact:
Mary Hale
Technical Info. Specialist
CM1 12D16 Tel: 308-4258



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PTO-1590 (2-99)

Srpada
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STRUCTURE FILE UPDATES: 10 SEP 99 HIGHEST RN 238435-06-8
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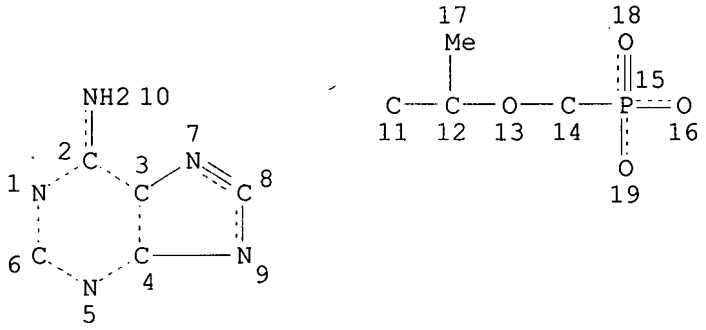

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DEFAULT ECLEVEL IS LIMITED

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STEREO ATTRIBUTES: NONE
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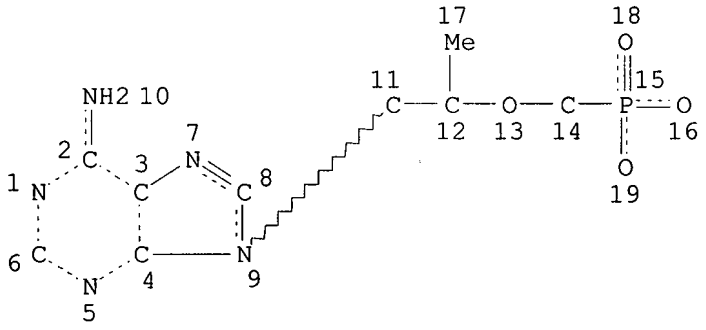

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100.0% PROCESSED 47 ITERATIONS 45 ANSWERS
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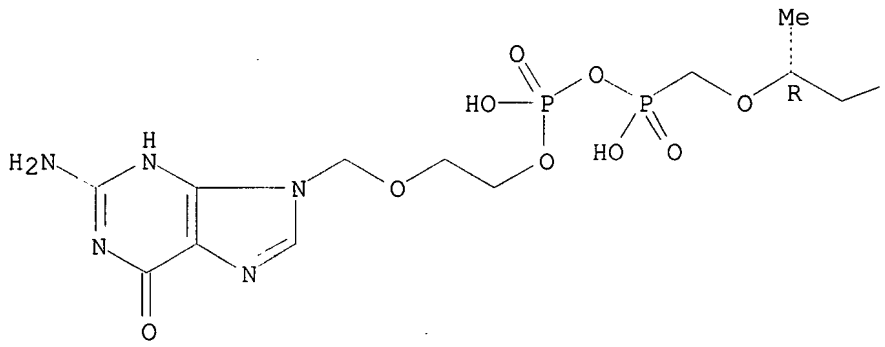
RN 238411-89-7 REGISTRY
CN INDEX NAME NOT YET ASSIGNED
FS STEREOSEARCH
MF C17 H24 N10 O9 P2
SR CA
LC STN Files: CAPLUS

Absolute stereochemistry.

PAGE 1-A



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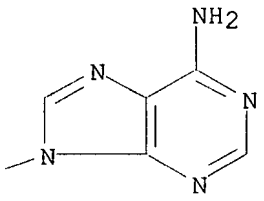
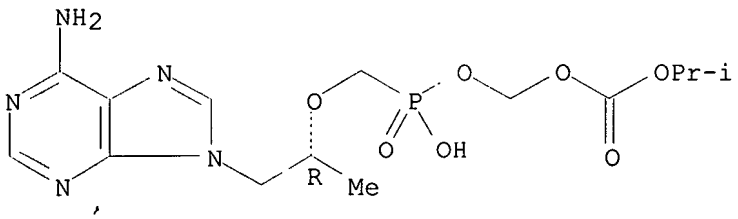


1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L5 ANSWER 2 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 211364-69-1 REGISTRY
CN Carbonic acid, [[[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]hydroxyphosphinyl]oxy]methyl 1-methylethyl ester (9CI)
(CA INDEX NAME)
FS STEREOSEARCH

MF C14 H22 N5 O7 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

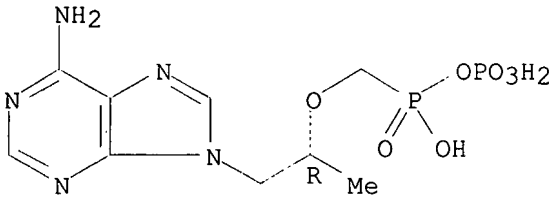
REFERENCE 1: 129:170075 Antiretroviral efficacy and pharmacokinetics of oral bis(isopropyloxycarbonyloxymethyl)-9-(2-phosphonylmethoxypropyl)adenine in mice. Naesens, Lieve; Bischofberger, Norbert; Augustijns, Patrick; Annaert, Pieter; Van Den Mooter, Guy; Arimilli, Murty N.; Kim, Choung U.; De Clercq, Erik (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.). Antimicrob. Agents Chemother., 42(7), 1568-1673 (English) 1998. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.

AB To overcome the low oral bioavailability of the highly potent and selective antiretroviral agent (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), its lipophilic ester deriv. bis(isopropyloxycarbonyloxymethyl)-ester [bis(POC)-PMPA] was prepd. The usefulness of bis(POC)-PMPA as an oral prodrug for PMPA was investigated in the intestinal mucosa Caco-2 cell monolayer model. The total transport of bis(POC)-PMPA was 2.7%, whereas it was <0.1% for PMPA. Bis(POC)-PMPA was considerably metabolized inside the epithelial cells, since the majority of the compd. was recovered after transport in the form of the monoester metabolite mono(POC)-PMPA. Bis(POC)-PMPA was relatively resistant to degrdn. at the luminal side of the Caco-2 cells. Pharmacokinetic studies in mice showed that the oral bioavailability of bis(POC)-PMPA calcd. from the curves of the concn. of free PMPA in blood plasma was 20%. Neither bis(POC)-PMPA nor mono(POC)-PMPA could be recovered from blood plasma, suggesting the efficient release of the active drug PMPA after oral administration of bis(POC)-PMPA. Severe combined immunodeficient (SCID) mice infected with Moloney murine sarcoma virus (MSV) and treated orally with bis(POC)-PMPA for 5 or 10 days at dosages of 50, 100, or 200 mg PMPA equiv./kg/day showed a significant delay in MSV-induced tumor appearance and tumor-assocd. death. The antiviral efficacy of oral bis(POC)-PMPA was related to the dosage and treatment period and was not significantly different from that of s.c. PMPA given at equiv. doses. The favorable pharmacokinetic profile, marked antiviral efficacy, and low toxicity make bis(POC)-PMPA an attractive oral prodrug of PMPA that should be pursued in clin. studies in patients infected with human immunodeficiency virus or hepatitis B virus.

L5 ANSWER 3 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 206646-04-0 REGISTRY
CN Phosphoric acid, monoanhydride with [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:
CN Phosphoric acid, monoanhydride with [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid, (R)-
FS STEREOSEARCH
MF C9 H15 N5 O7 P2
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:60635 Selective inhibition of HIV-1 reverse transcriptase by an antiviral inhibitor, (R)-9-(2-phosphonylmethoxypropyl)adenine. Suo, Zucai; Johnson, Kenneth A. (Department of Biochemistry and Molecular Biology, the Pennsylvania State University, University Park, PA, 16802, USA). J. Biol. Chem., 273(42), 27250-27258 (English) 1998. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB (R)-9-(2-Phosphonylmethoxypropyl)adenine (PMPA) is an acyclic nucleoside phosphonate that has been shown to be effective in the treatment of AIDS although it has a shorter sepn. between the adenine and phosphorus than dideoxy-AMP and dAMP. By using presteady state kinetic methods, we examd. the incorporation of the diphosphate of PMPA, 2',3'-dideoxyadenosine 5'-triphosphate (ddATP), and dATP catalyzed by wild-type human immunodeficiency virus type 1 (HIV-1) reverse transcriptase, an exonuclease-deficient T7 DNA polymerase (T7 exo-), and wild-type rat DNA polymerase .beta. to evaluate the selectivity of PMPA as an antiviral inhibitor. With a DNA/DNA or DNA/RNA 22/43-mer duplex, the diphosphate of PMPA (PMPApp) is as effective as ddATP in reactions catalyzed by HIV-1 reverse transcriptase in that both analogs have similar substrate specificity consts. (kp/Kd) which are only 5-fold lower than dATP. In contrast, PMPApp is a much weaker inhibitor of the reaction catalyzed by T7 exo- (with the DNA/DNA 22/43-mer duplex) in that PMPApp has a 5.times.10-4-fold lower kp/Kd than ddATP and dATP. The lower kp/Kd of PMPApp is due to a 1000-2000-fold lower incorporation rate (kp) and a 35-45-fold lower binding const. (Kd). Similarly, PMPApp is 800-fold less inhibitory toward polymerase .beta. with the DNA/DNA 22/43-mer duplex, whereas in studies with a single nucleotide gapped DNA (22-20/43-mer) PMPApp is 13-fold less inhibitory than ddATP. Although parallel studies will need to be performed using appropriate human polymerases, these results begin to define the mechanistic basis for the reported lower toxicity of PMPA in the treatment of AIDS.

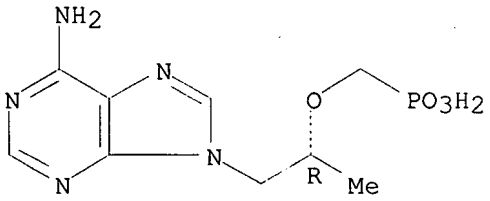
REFERENCE 2: 128:303669 Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-R-(2-phosphonomethoxypropyl)adenine (PMPA), bis(isopropyloxymethylcarbonyl)PMPA. Robbins, Brian L.; Srinivas, Ranga

V.; Kim, Choung; Bischofberger, Norbert; Fridland, Arnold (Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA). Antimicrob. Agents Chemother., 42(3), 612-617 (English) 1998. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.

AB Bis(isopropyloxymethylcarbonyl) 9-R-(2-phosphonomethoxypropyl)adenine [bis(POC)PMPA] has been identified as a novel prodrug of PMPA. The anti-human immunodeficiency virus activity of bis(POC)PMPA was >100-fold greater than that of PMPA in both an established T-cell line and primary peripheral blood lymphocytes. This improved efficacy was shown to be due to a rapid intracellular uptake of the prodrug resulting in an increased intracellular accumulation of PMPA diphosphate (PMPApp), the pharmacol. active metabolite. PMPApp levels in bis(POC)PMPA-treated cells exceeded by >1000-fold the levels seen in cells treated with unmodified PMPA in both resting and activated peripheral blood lymphocytes. Significant differences in the intracellular catabolism of PMPA metabolites were noted between the resting and activated lymphocytes. The half-life for the disappearance of PMPApp, derived from either bis(POC)PMPA or PMPA, was 12 to 15 h in the activated lymphocytes and 33 to 50 h in the resting lymphocytes. This long persistence of PMPApp, particularly in resting lymphocytes, may be unique to the nucleoside phosphonate analogs and indicates that effective levels of the active metabolite can be achieved and maintained with relatively infrequent administration of the parent drug.

L5 ANSWER 4 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 206184-49-8 REGISTRY
CN Phosphonic acid, [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, monohydrate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, monohydrate, (R)-
FS STEREOSEARCH
MF C9 H14 N5 O4 P . H2 O
SR US Adopted Names Council
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL
CRN (147127-20-6)

Absolute stereochemistry.



● H_2O

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:158419 Antiviral nucleotide analog composition and synthesis method. Munger, John D., Jr.; Rohloff, John C.; Schultze, Lisa M. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9905150 A1 19990204,

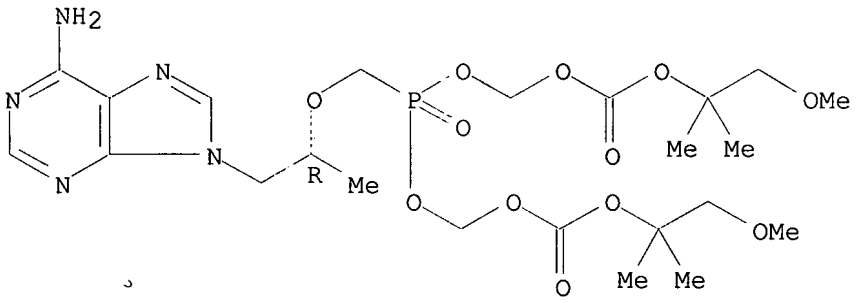
43 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US15254 19980723. PRIORITY: US 1997-900752 19970725; US 1997-53777 19970725.

AB The invention provides a compn. comprising 9-[2-(R)-[[Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]adenine [bis(POC)PMPA] and fumaric acid (1:1) for oral delivery of (R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA). The compn. is useful as an intermediate for the prepn. of antiviral compds., or is useful for administration to patients for antiviral therapy or prophylaxis. The compn. is particularly useful when administered orally. The invention also provides methods to make PMPA and intermediates in PMPA synthesis. Embodiments include lithium t-butoxide, 9-(2-hydroxypropyl)adenine and di-Et p-toluenesulfonylmethoxy-phosphonate in an org. solvent such as DMF.

The reaction results in di-Et PMPA prepns. contg. an improved byproduct profile compared to di-Et PMPA made by prior methods. "Bis(POC)PMPA" fumarate, or BPPF, was prepd. in 7 steps via reaction of (R)-4-methyl-1,3-dioxolan-2-one with adenine and etherification of the product with (EtO)2P(O)CH2-OTs.

L5 ANSWER 5 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 202138-54-3 REGISTRY
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2-methoxy-1,1-dimethylethyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H38 N5 O12 P
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

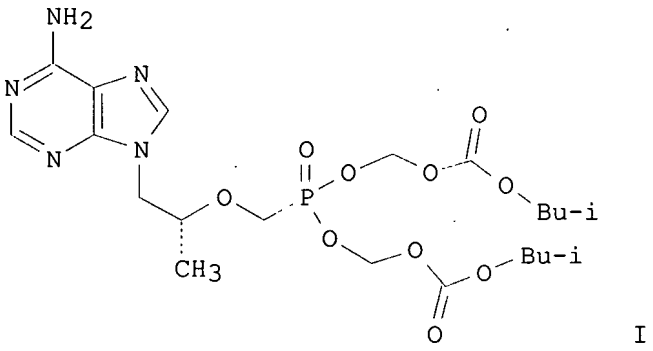


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74

pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

GI



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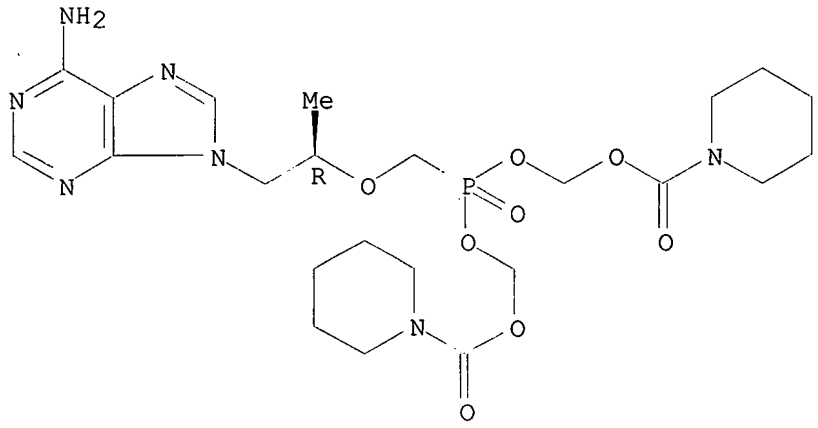
AB Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn. of antiviral compds. or oligonucleotides, or are useful for administration directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

L5 ANSWER 6 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 202138-53-2 REGISTRY
CN 1-Piperidinecarboxylic acid, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H36 N7 O8 P
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

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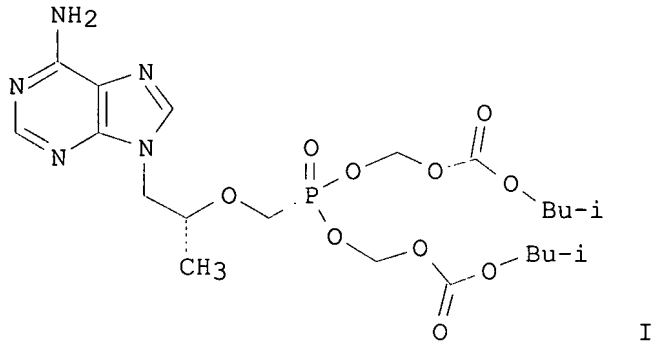


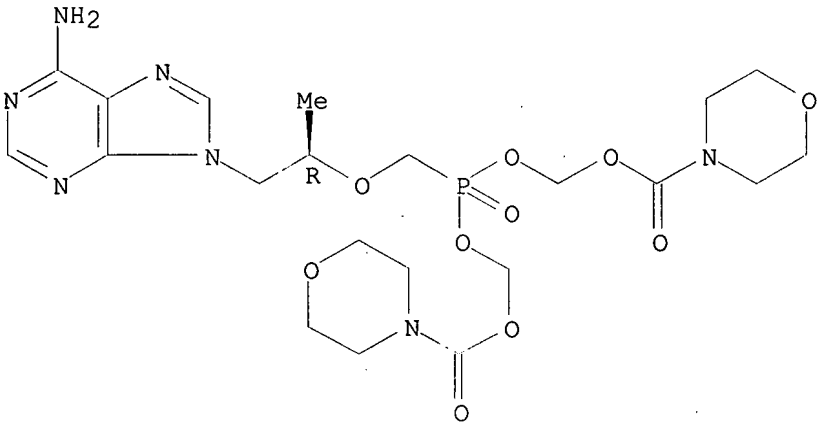
I

AB Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or

C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn.
of antiviral compds. or oligonucleotides, or are useful for administration
directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

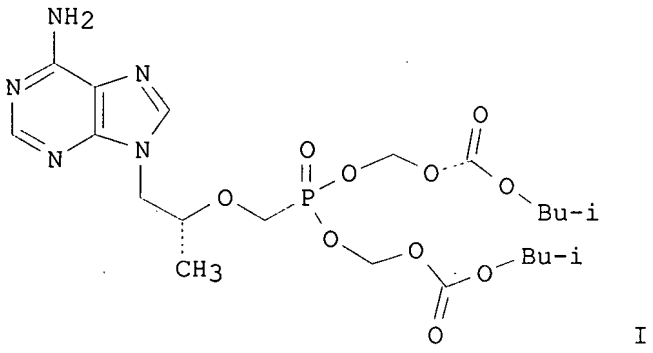
L5 ANSWER 7 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 202138-52-1 REGISTRY
CN 4-Morpholinecarboxylic acid, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H32 N7 O10 P
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.
GI

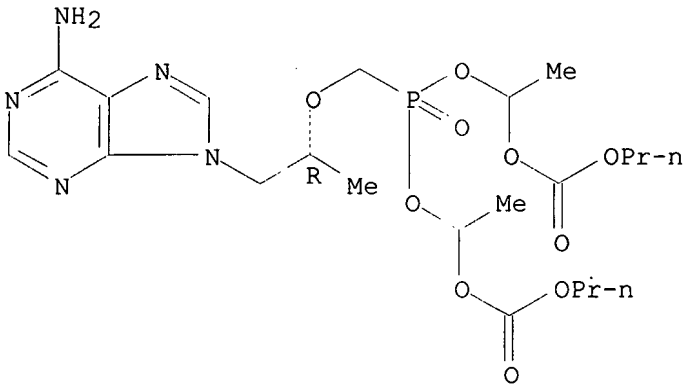


I

AB Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn. of antiviral compds. or oligonucleotides, or are useful for administration directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

L5 ANSWER 8 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 202138-51-0 REGISTRY
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-3,7-dimethyl-, dipropyl ester, 5-oxide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-3,7-dimethyl-, dipropyl ester, 5-oxide, stereoisomer
FS STEREOSEARCH
MF C21 H34 N5 O10 P
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

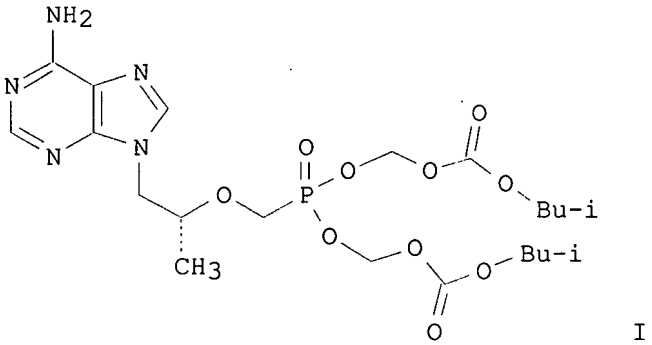
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

GI



I

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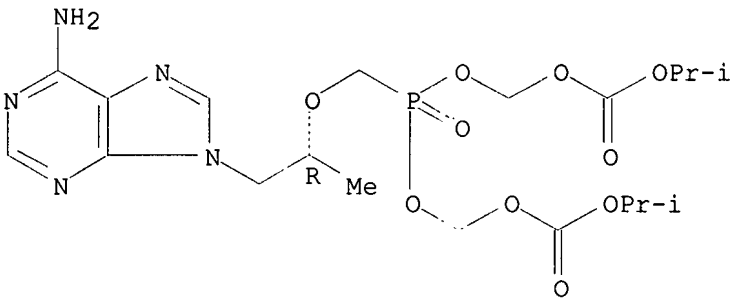
the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn.
of antiviral compds. or oligonucleotides, or are useful for administration
directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

L5 ANSWER 9 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 202138-50-9 REGISTRY
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide, (R)-, (E)-2-butenedioate (1:1)
FS STEREOSEARCH
MF C19 H30 N5 O10 P . C4 H4 O4
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

CM 1

CRN 201341-05-1
CMF C19 H30 N5 O10 P

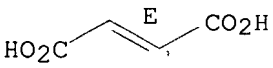
Absolute stereochemistry.



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:158419 Antiviral nucleotide analog composition and synthesis method. Munger, John D., Jr.; Rohloff, John C.; Schultze, Lisa M. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9905150 A1 19990204, 43 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US15254 19980723. PRIORITY: US 1997-900752 19970725; US 1997-53777 19970725.

AB The invention provides a compn. comprising 9-[2-(R)-[[Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]adenine [bis(POC)PMPA] and fumaric acid (1:1) for oral delivery of (R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA). The compn. is useful as an intermediate for the prepn. of antiviral compds., or is useful for administration to patients for antiviral therapy or prophylaxis. The compn. is particularly useful when administered orally. The invention also provides methods to make PMPA and intermediates in PMPA synthesis. Embodiments include lithium t-butoxide, 9-(2-hydroxypropyl)adenine and di-Et p-toluenesulfonylmethoxy-phosphonate in an org. solvent such as DMF.

The reaction results in di-Et PMPA prepns. contg. an improved byproduct profile compared to di-Et PMPA made by prior methods. "Bis(POC)PMPA" fumarate, or BPPF, was prepd. in 7 steps via reaction of (R)-4-methyl-1,3-dioxolan-2-one with adenine and etherification of the product with (EtO)2P(O)CH2-OTs.

REFERENCE 2: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

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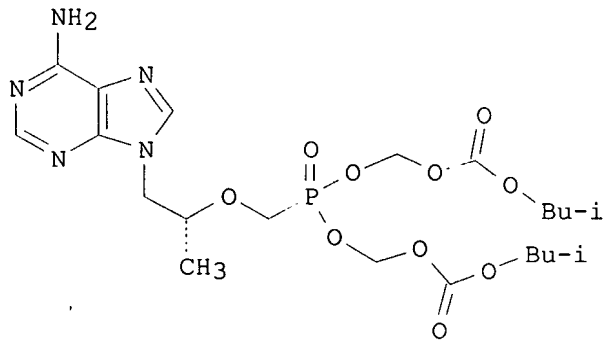

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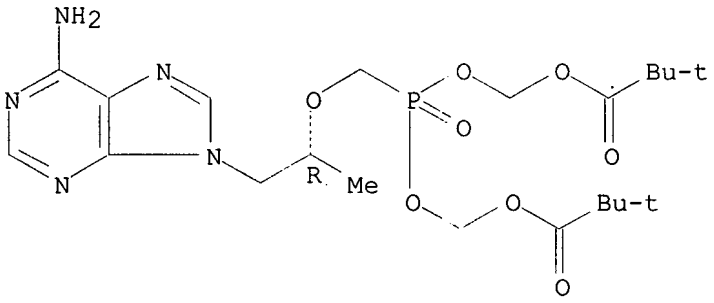
of antiviral compds. or oligonucleotides, or are useful for administration
directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

L5 ANSWER 10 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201341-13-1 REGISTRY
CN Propanoic acid, 2,2-dimethyl-, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H34 N5 O8 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:196530 Metabolism and pharmacokinetics of novel oral prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs. Shaw, Jeng-Pyng; Sueoka, Cathy M.; Oliyai, Reza; Lee, William A.; Arimilli, Murty N.; Kim, Choung U.; Cundy, Kenneth C. (Gilead Sciences, Inc., Foster City, CA, 94404, USA). Pharm. Res., 14(12), 1824-1829 (English) 1997. CODEN: PHREEB. ISSN: 0724-8741. Publisher: Plenum Publishing Corp..
AB A series of prodrugs designed to enhance the oral bioavailability of the antiretroviral agent 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) have

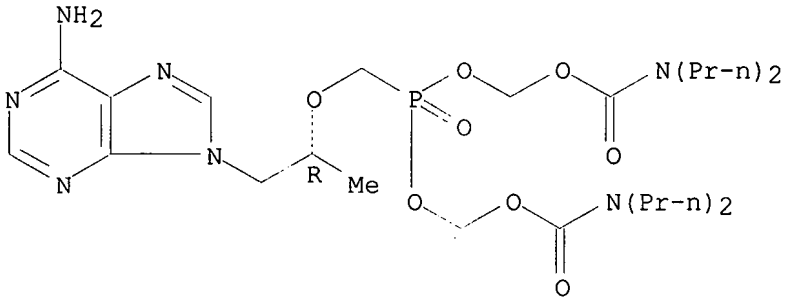
been synthesized, including a bis-(acyloxymethyl) ester and a series of bis-(alkoxycarbonyloxymethyl) esters. All prodrugs were rapidly hydrolyzed in dog plasma and tissues (t1/2 <60 min). In fasted beagle dogs, bis[(pivaloyloxy)methyl] PMPA (bis-POM PMPA) had the highest oral bioavailability as PMPA (37.8 .+-. 5.1%). The oral bioavailabilities of PMPA from bis(alkoxycarbonyloxymethyl) esters ranged from 16.0% to 30.7% and PMPA was the major metabolite formed. There was a correlation between oral bioavailability and intestinal stability of bis(alkoxycarbonyloxymethyl) ester prodrugs (r2 = 0.96). Lipophilicity (log P) was not a good predictor of oral bioavailability. The most labile prodrugs in dog intestinal homogenates, bis(n-butyloxycarbonyloxymethyl) PMPA and bis-(neopentyloxycarbonyloxymethyl) PMPA (t1/2 <5 min) had the lowest oral bioavailabilities. Based on good oral bioavailability (30.1%), chem. and intestinal stability bis(isopropyloxycarbonyloxymethyl) PMPA (bis-POC PMPA) was selected as a candidate for clin. evaluation.

REFERENCE 2: 128:97300 Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. (Gilead Sci., Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 8(6), 557-564 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB Potentially orally bioavailable prodrugs of the antiretroviral agent 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) were evaluated. Alkyl Me carbamates were synthesized by alkylation of PMPA with the corresponding alkyl chloromethyl carbonate and N-alkyl chloromethyl carbamate reagents. The prodrugs were evaluated for in vitro antiviral activity in addn. to chem. and enzymic stability. The inhibition of human immunodeficiency virus type 1 (HIV-1) strain IIIB replication of MT-2 cells by the carbonate prodrugs was found to be 2.5-500-fold increased compared to PMPA. The alkyl Me carbonates, except t-Bu Me carbonate, had reasonable chem. stability at pH 2.2 and 7.4, but were rapidly converted to the corresponding monoester of PMPA in the presence of dog plasma. The alkyl Me carbamate prodrugs such a N-t-Bu Me carbamate were found to have high stability in vitro. Based on its chem. stability and good oral bioavailability, bis(POC)PMPA (iso-Pr methylcarbonate) was chosen as a clin. candidate.

L5 ANSWER 11 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201341-11-9 REGISTRY
CN Carbamic acid, dipropyl-, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H44 N7 O8 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

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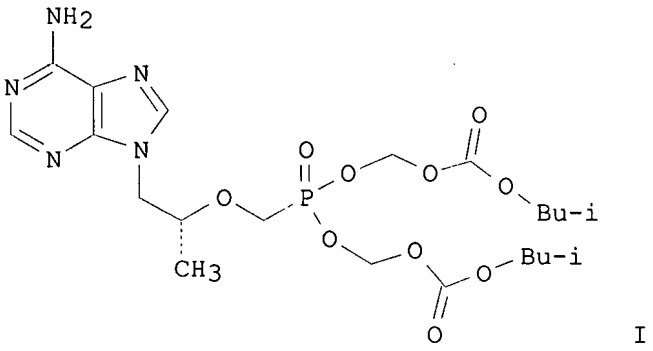


I

AB Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn.

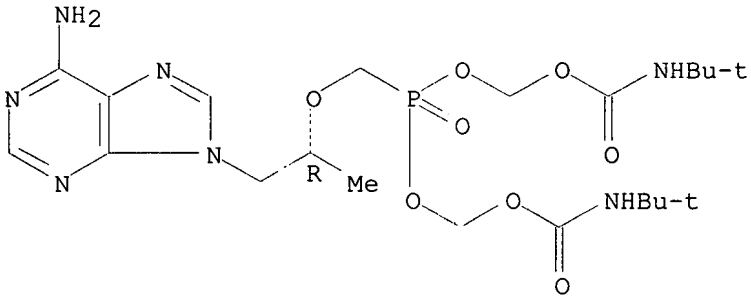
of antiviral compds. or oligonucleotides, or are useful for administration
directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

REFERENCE 2: 128:97300 Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. (Gilead Sci., Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 8(6), 557-564 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB Potentially orally bioavailable prodrugs of the antiretroviral agent 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) were evaluated. Alkyl Me carbamates were synthesized by alkylation of PMPA with the corresponding alkyl chloromethyl carbonate and N-alkyl chloromethyl carbamate reagents. The prodrugs were evaluated for in vitro antiviral activity in addn. to chem. and enzymic stability. The inhibition of human immunodeficiency virus type 1 (HIV-1) strain IIIB replication of MT-2 cells by the carbonate prodrugs was found to be 2.5-500-fold increased compared to PMPA. The alkyl Me carbonates, except t-Bu Me carbonate, had reasonable chem. stability at pH 2.2 and 7.4, but were rapidly converted to the corresponding monoester of PMPA in the presence of dog plasma. The alkyl Me carbamate prodrugs such a N-t-Bu Me carbamate were found to have high stability in vitro. Based on its chem. stability and good oral bioavailability, bis(POC)PMPA (iso-Pr methylcarbonate) was chosen as a clin. candidate.

L5 ANSWER 12 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201341-09-5 REGISTRY
CN Carbamic acid, (1,1-dimethylethyl)-, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H36 N7 O8 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74

pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

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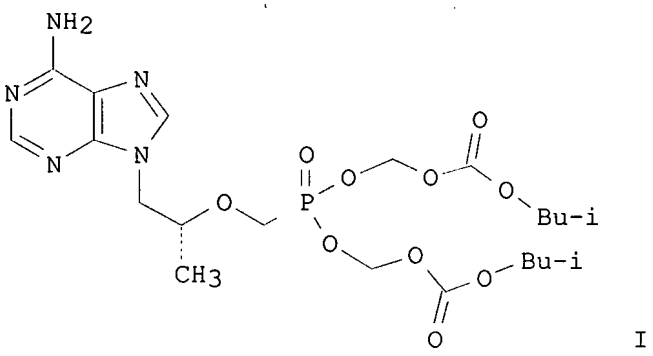

I

AB Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn.
of antiviral compds. or oligonucleotides, or are useful for administration
directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

REFERENCE 2: 128:97300 Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. (Gilead Sci., Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 8(6), 557-564 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

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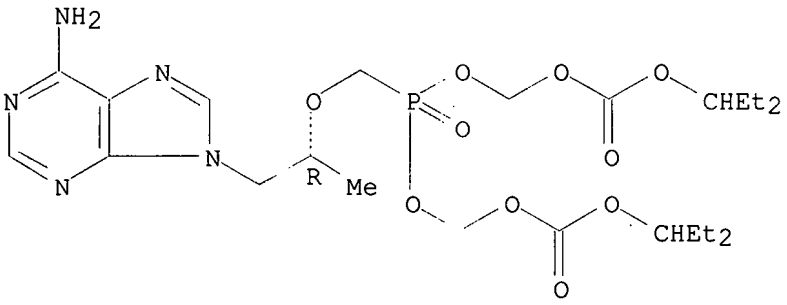
L5 ANSWER 13 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201341-07-3 REGISTRY
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid,
5-[[2-(6-amino-9H-purin-9-yl)-
1-methylethoxy]methyl]-, bis(1-ethylpropyl) ester, 5-oxide, (R)- (9CI)
(CA INDEX NAME)
FS STEREOSEARCH
MF C23 H38 N5 O10 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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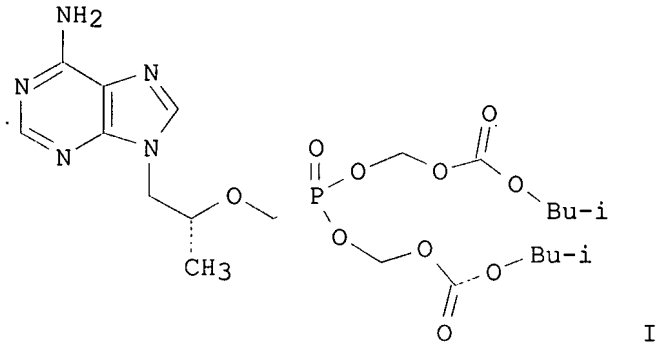
PMPA and bis-(neopentyloxycarbonyloxymethyl) PMPA (t1/2 <5 min) had the lowest oral bioavailabilities. Based on good oral bioavailability (30.1%), chem. and intestinal stability
bis(isopropyloxycarbonyloxymethyl)
PMPA (bis-POC PMPA) was selected as a candidate for clin. evaluation.

REFERENCE 2: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

GI



I

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of antiviral compds. or oligonucleotides, or are useful for administration
directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

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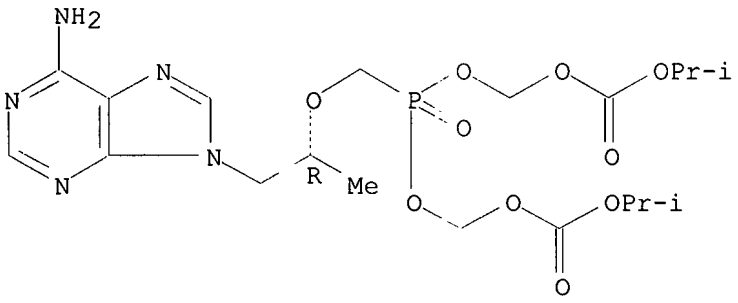
AB Potentially orally bioavailable prodrugs of the antiretroviral agent 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) were evaluated. Alkyl Me carbamates were synthesized by alkylation of PMPA with the corresponding alkyl chloromethyl carbonate and N-alkyl chloromethyl carbamate reagents. The prodrugs were evaluated for in vitro antiviral activity in addn. to chem. and enzymic stability. The inhibition of human immunodeficiency virus type 1 (HIV-1) strain IIIB replication of MT-2 cells by the carbonate prodrugs was found to be 2.5-500-fold increased compared to PMPA. The alkyl Me carbonates, except t-Bu Me carbonate, had reasonable chem. stability at pH 2.2 and 7.4, but were rapidly converted to the corresponding monoester of PMPA in the presence of dog plasma. The alkyl Me carbamate prodrugs such a N-t-Bu Me carbamate were found to have high stability in vitro. Based on its chem. stability and good oral bioavailability, bis(POC)PMPA (iso-Pr methylcarbonate) was chosen as a clin. candidate.

L5 ANSWER 14 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201341-05-1 REGISTRY
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, 5-oxide, (R)-
FS STEREOSEARCH
MF C19 H30 N5 O10 P
CI COM
SR CA
LC STN Files: ADISINSIGHT, CA, CAPLUS, IPA, TOXLINE, TOXLIT, USPATFULL

Absolute stereochemistry.



7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:296895 (R)-PMPA and Bis(POC)PMPA: Anti-HIV. Sorbera, L. A.; Castaner, J. (Prous Science, Barcelona, 08080, Spain). Drugs Future, 23(12), 1279-1286 (English) 1998. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.

AB Review with 40 refs. on the synthesis and pharmaciol. of the title compds.

REFERENCE 2: 129:170075 Antiretroviral efficacy and pharmacokinetics of oral

bis(isopropyloxycarbonyloxymethyl)-9-(2-phosphonylmethoxypropyl)adenine in
mice. Naesens, Lieve; Bischofberger, Norbert; Augustijns, Patrick; Annaert, Pieter; Van Den Mooter, Guy; Arimilli, Murty N.; Kim, Choung U.; De Clercq, Erik (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.). Antimicrob. Agents Chemother., 42(7), 1568-1673 (English) 1998. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.

AB To overcome the low oral bioavailability of the highly potent and selective antiretroviral agent (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), its lipophilic ester deriv. bis(isopropyloxycarbonyloxymethyl)-ester [bis(POC)-PMPA] was prepd. The usefulness of bis(POC)-PMPA as an oral prodrug for PMPA was investigated in the intestinal mucosa Caco-2 cell monolayer model. The total transport of bis(POC)-PMPA was 2.7%, whereas it was <0.1% for PMPA. Bis(POC)-PMPA was considerably metabolized inside the epithelial cells, since the majority of the compd. was recovered after transport in the form of the monoester metabolite mono(POC)-PMPA. Bis(POC)-PMPA was relatively resistant to degrdn. at the luminal side of the Caco-2 cells. Pharmacokinetic studies in mice showed that the oral bioavailability of bis(POC)-PMPA calcd. from the curves of the concn. of free PMPA in blood plasma was 20%. Neither bis(POC)-PMPA nor mono(POC)-PMPA could be recovered from blood plasma, suggesting the efficient release of the active drug PMPA after oral administration of bis(POC)-PMPA. Severe combined immunodeficient (SCID) mice infected with Moloney murine sarcoma virus (MSV) and treated orally with bis(POC)-PMPA for 5 or 10 days at dosages of 50, 100, or 200 mg PMPA equiv./kg/day showed a significant delay in MSV-induced tumor appearance and tumor-assocd. death. The antiviral efficacy of oral bis(POC)-PMPA was related to the dosage and treatment period and was not significantly different from that of s.c. PMPA given at equiv. doses. The favorable pharmacokinetic profile, marked antiviral efficacy, and low toxicity make bis(POC)-PMPA an attractive oral prodrug of PMPA that should be pursued in clin. studies in patients infected with human immunodeficiency virus or hepatitis B virus.

REFERENCE 3: 129:117461 Antiviral activities of 9-R-2-phosphonomethoxypropyl
adenine (PMPA) and bis(isopropyloxymethylcarbonyl)PMPA against various drug-resistant human immunodeficiency virus strains. Srinivas, Ranga V.; Fridland, Arnold (Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA). Antimicrob. Agents Chemother., 42(6), 1484-1487 (English) 1998. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.

AB 9-R-2-Phosphonomethoxypropyl adenine (PMPA) is an acyclic nucleoside phosphonate analog with efficacy against human immunodeficiency virus (HIV). We recently described the synthesis, metab., and biol. activities of bis(isopropyloxymethylcarbonyl)PMPA [bis(poc)PMPA] as an orally bioavailable prodrug for PMPA. Among a large panel of drug-resistant HIV type 1 variants, only the K65R virus was resistant to PMPA. The K65R virus also showed reduced susceptibility to bis(poc)PMPA, although the prodrug could still inhibit these viruses at nontoxic submicromolar concns. In a panel of 7 primary clin. isolates from patients with diverse treatment histories, only one isolate showed reduced susceptibility to PMPA and was found to carry 3 mutations (M41L, T69N, R73K) in its reverse transcriptase catalytic domain.

REFERENCE 4: 128:303669 Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside

phosphonate 9-R-(2-phosphonomethoxypropyl)adenine (PMPA), bis(isopropyloxymethylcarbonyl)PMPA. Robbins, Brian L.; Srinivas, Ranga V.; Kim, Choung; Bischofberger, Norbert; Fridland, Arnold (Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA). Antimicrob. Agents Chemother., 42(3), 612-617 (English) 1998. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.

AB Bis(isopropyloxymethylcarbonyl) 9-R-(2-phosphonomethoxypropyl)adenine [bis(POC)PMPA] has been identified as a novel prodrug of PMPA. The anti-human immunodeficiency virus activity of bis(POC)PMPA was >100-fold greater than that of PMPA in both an established T-cell line and primary peripheral blood lymphocytes. This improved efficacy was shown to be due to a rapid intracellular uptake of the prodrug resulting in an increased intracellular accumulation of PMPA diphosphate (PMPApp), the pharmacol. active metabolite. PMPApp levels in bis(POC)PMPA-treated cells exceeded by >1000-fold the levels seen in cells treated with unmodified PMPA in both resting and activated peripheral blood lymphocytes. Significant differences in the intracellular catabolism of PMPA metabolites were noted between the resting and activated lymphocytes. The half-life for the disappearance of PMPApp, derived from either bis(POC)PMPA or PMPA, was 12 to 15 h in the activated lymphocytes and 33 to 50 h in the resting lymphocytes. This long persistence of PMPApp, particularly in resting lymphocytes, may be unique to the nucleoside phosphonate analogs and indicates that effective levels of the active metabolite can be achieved and maintained with relatively infrequent administration of the parent drug.

REFERENCE 5: 128:196530 Metabolism and pharmacokinetics of novel oral prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs. Shaw, Jeng-Pyng; Sueoka, Cathy M.; Oliyai, Reza; Lee, William A.; Arimilli, Murty N.; Kim, Choung U.; Cundy, Kenneth C. (Gilead Sciences, Inc., Foster City, CA, 94404, USA). Pharm. Res., 14(12), 1824-1829 (English) 1997. CODEN: PHREEB. ISSN: 0724-8741. Publisher: Plenum Publishing Corp..

AB A series of prodrugs designed to enhance the oral bioavailability of the antiretroviral agent 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) have been synthesized, including a bis-(acyloxymethyl) ester and a series of bis-(alkoxycarbonyloxymethyl) esters. All prodrugs were rapidly hydrolyzed in dog plasma and tissues (t1/2 <60 min). In fasted beagle dogs, bis[(pivaloyloxy)methyl] PMPA (bis-POM PMPA) had the highest oral bioavailability as PMPA (37.8 .+-. 5.1%). The oral bioavailabilities of PMPA from bis(alkoxycarbonyloxymethyl) esters ranged from 16.0% to 30.7% and PMPA was the major metabolite formed. There was a correlation between oral bioavailability and intestinal stability of bis(alkoxycarbonyloxymethyl) ester prodrugs (r2 = 0.96). Lipophilicity (log P) was not a good predictor of oral bioavailability. The most labile prodrugs in dog intestinal homogenates, bis(n-butyloxycarbonyloxymethyl) PMPA and bis-(neopentyloxycarbonyloxymethyl) PMPA (t1/2 <5 min) had the lowest oral bioavailabilities. Based on good oral bioavailability (30.1%), chem. and intestinal stability bis(isopropyloxycarbonyloxymethyl) PMPA (bis-POC PMPA) was selected as a candidate for clin. evaluation.

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pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

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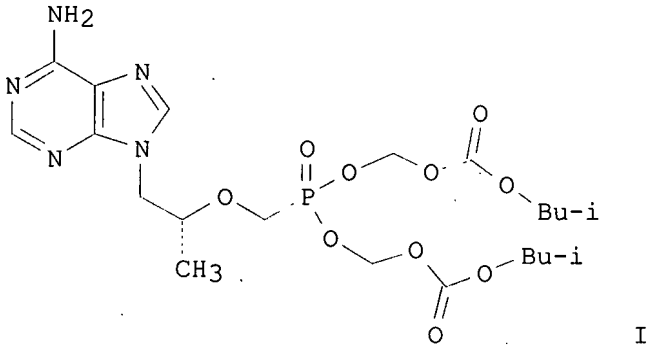

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L5 ANSWER 15 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201341-03-9 REGISTRY
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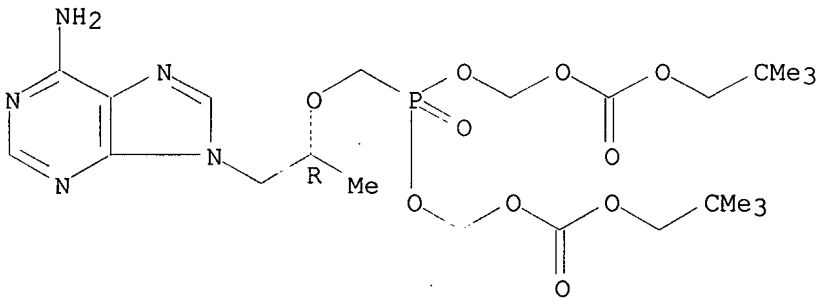
FS STEREOSEARCH
MF C23 H38 N5 O10 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



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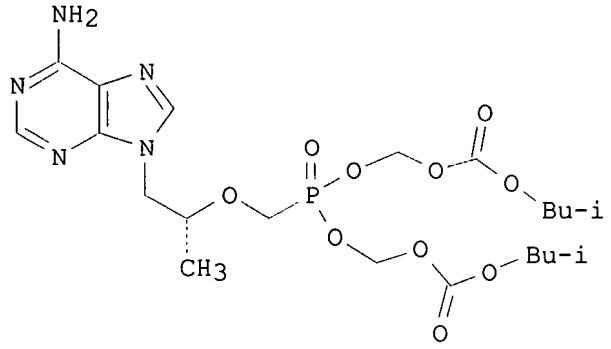

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L5 ANSWER 16 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201341-01-7 REGISTRY
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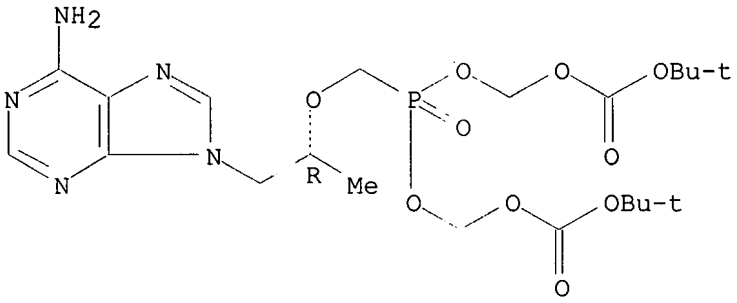
(CA INDEX NAME)
FS STEREOSEARCH
MF C21 H34 N5 O10 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



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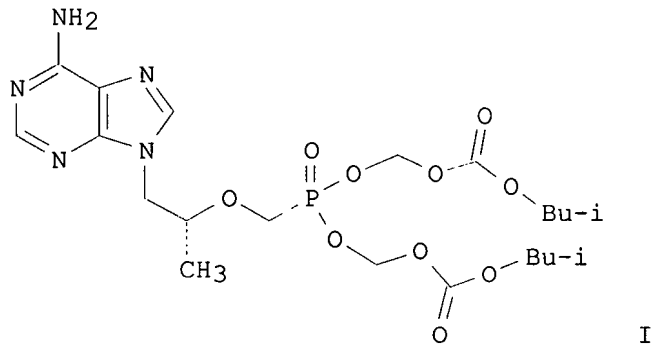
GI



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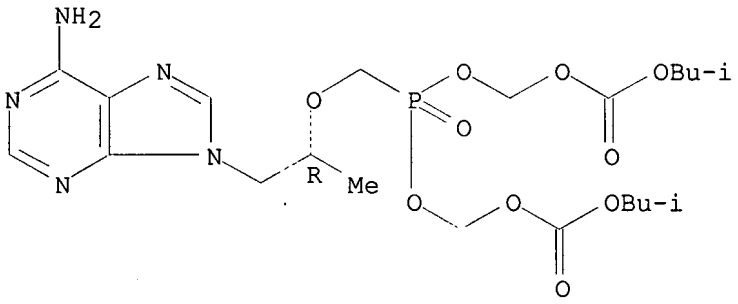
L5 ANSWER 17 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201340-99-0 REGISTRY
CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid, 5-[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(2-methylpropyl) ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C21 H34 N5 O10 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



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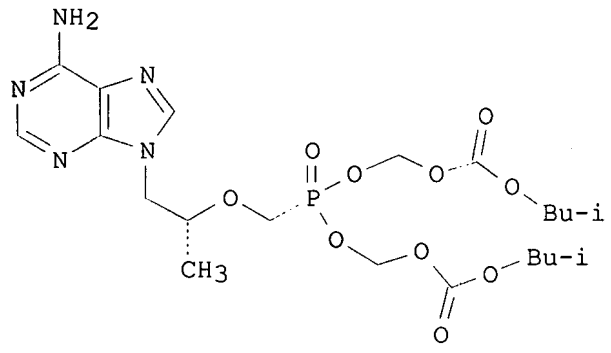

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L5 ANSWER 18 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201340-97-8 REGISTRY
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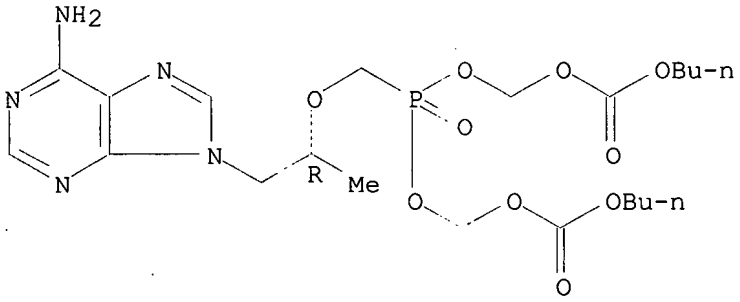
FS STEREOSEARCH
MF C21 H34 N5 O10 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



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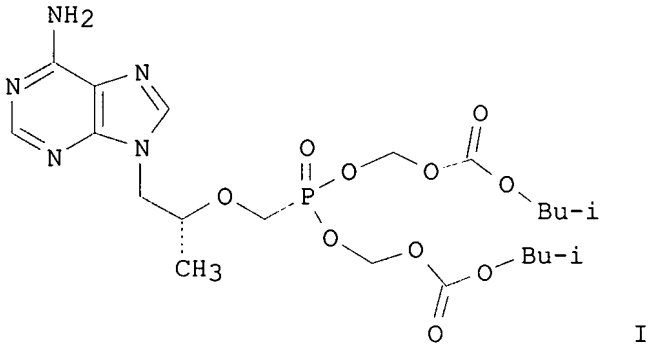

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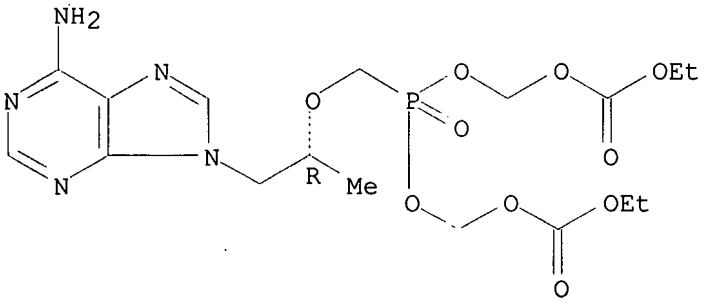
L5 ANSWER 19 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 201340-95-6 REGISTRY

CN 2,4,6,8-Tetraoxa-5-phosphanonanedioic acid,
5-[[2-(6-amino-9H-purin-9-yl)-
1-methylethoxy]methyl]-, diethyl ester, 5-oxide, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C17 H26 N5 O10 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

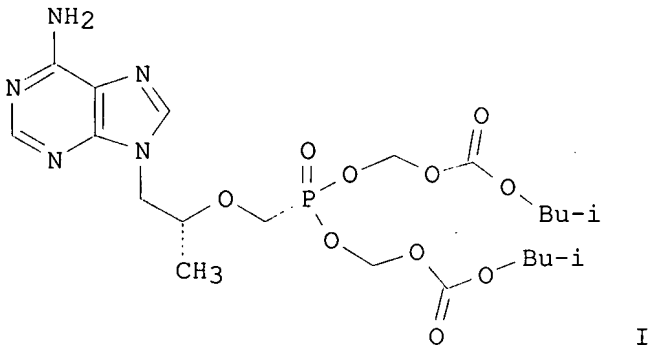
REFERENCE 1: 128:196530 Metabolism and pharmacokinetics of novel oral prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs. Shaw, Jeng-Pyng; Sueoka, Cathy M.; Oliyai, Reza; Lee, William A.; Arimilli, Murty N.; Kim, Choung U.; Cundy, Kenneth C. (Gilead Sciences, Inc., Foster City, CA, 94404, USA). Pharm. Res., 14(12), 1824-1829 (English) 1997. CODEN: PHREEB. ISSN: 0724-8741. Publisher: Plenum Publishing Corp..

AB A series of prodrugs designed to enhance the oral bioavailability of the antiretroviral agent 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) have been synthesized, including a bis-(acyloxymethyl) ester and a series of bis-(alkoxycarbonyloxymethyl) esters. All prodrugs were rapidly hydrolyzed in dog plasma and tissues (t1/2 <60 min). In fasted beagle dogs, bis[(pivaloyloxy)methyl] PMPA (bis-POM PMPA) had the highest oral bioavailability as PMPA (37.8 .+-. 5.1%). The oral bioavailabilities of PMPA from bis(alkoxycarbonyloxymethyl) esters ranged from 16.0% to 30.7% and PMPA was the major metabolite formed. There was a correlation between oral bioavailability and intestinal stability of bis(alkoxycarbonyloxymethyl) ester prodrugs (r2 = 0.96). Lipophilicity (log P) was not a good predictor of oral bioavailability. The most labile prodrugs in dog intestinal homogenates, bis(n-butyloxycarbonyloxymethyl) PMPA and bis-(neopentyloxycarbonyloxymethyl) PMPA (t1/2 <5 min) had the lowest oral bioavailabilities. Based on good oral bioavailability (30.1%), chem. and intestinal stability bis(isopropyloxycarbonyloxymethyl) PMPA (bis-POC PMPA) was selected as a candidate for clin. evaluation.

REFERENCE 2: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA,

CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

GI



I

AB Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn.
of antiviral compds. or oligonucleotides, or are useful for administration
directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

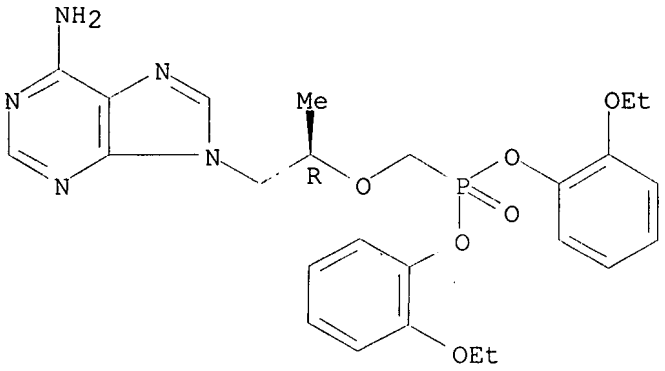
REFERENCE 3: 128:97300 Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs. Arimilli, M. N.; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. (Gilead Sci., Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 8(6), 557-564 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB Potentially orally bioavailable prodrugs of the antiretroviral agent 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) were evaluated. Alkyl Me carbamates were synthesized by alkylation of PMPA with the corresponding alkyl chloromethyl carbonate and N-alkyl chloromethyl carbamate reagents. The prodrugs were evaluated for in vitro antiviral activity in addn. to chem. and enzymic stability. The inhibition of human immunodeficiency virus type 1 (HIV-1) strain IIIB replication of MT-2 cells by the carbonate prodrugs was found to be 2.5-500-fold increased compared to

PMPA. The alkyl Me carbonates, except t-Bu Me carbonate, had reasonable chem. stability at pH 2.2 and 7.4, but were rapidly converted to the corresponding monoester of PMPA in the presence of dog plasma. The alkyl Me carbamate prodrugs such a N-t-Bu Me carbamate were found to have high stability in vitro. Based on its chem. stability and good oral bioavailability, bis(POC)PMPA (iso-Pr methylcarbonate) was chosen as a clin. candidate.

L5 ANSWER 20 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 193207-56-6 REGISTRY
CN Phosphonic acid,
[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-,
bis(2-ethoxyphenyl) ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-,
bis(2-ethoxyphenyl) ester, (R)-
FS STEREOSEARCH
MF C25 H30 N5 O6 P
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

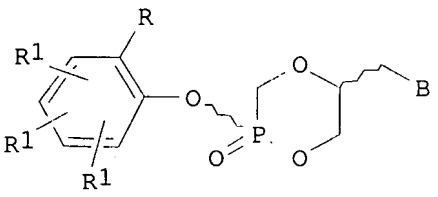
Absolute stereochemistry.



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:209927 Preparation of nucleotide phosphonate ester analogs as antiviral agents. Arimilli, Murty N.; Bischofberger, Norbert W.; Jones, Robert J.; Lee, William A.; Prisbe, Ernest J. (Gilead Sciences, Inc., USA). U.S. US 5886179 A 19990323, 36 pp., Cont.-in-part of U.S. Ser. No. 193,341, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1995-581147 19951229. PRIORITY: US 1993-123483 19930917; US 1994-193341 19940208.

GI

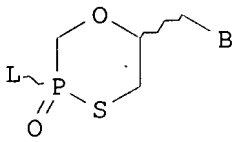


I

AB Nucleotide phosphonate esters I (B = 5-fluorocytosin-1-yl, 5-methylcytosin-1-yl, heterocycle; R = S(O2)N(R3)2; R1 = H,CN, nitro, alkyl, -O-alkyl, acyl, SO3H, amine, CHO; R3 = H, alkyl, Ph, substituted Ph) characterized by the presence of an ester linked group which is bonded to the phosphorus atom of phosphonate nucleotide analogs are prepd. as virucides. The analogs comprise an ester bond that is hydrolyzed in vivo to yield a corresponding phosphonate nucleotide analog. Thus, (R)-9-(2-di-2-ethoxyphenylphosphonylmethoxypropyl)adenine was prepd. and tested for its HSV-1 and HSV-2 antiviral activities (EC50 = 3 .mu.M).

REFERENCE 2: 129:189610 Preparation of amidate linked amino acid nucleotide analogs as antitumors and antiviral agents. Bischofberger, Norbert W.; Jones, Robert J.; Arimilli, Murty N.; Louie, Michael S.; Prisbe, Ernest J.; Lee, William A. (Gilead Sciences, Inc., USA). U.S. US 5798340 A 19980825, 62 pp. Cont.-in-part of U.S. Ser. No. 193,341, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1996-617849 19960506. PRIORITY: US 1993-123483 19930917; US 1994-193341 19940208; WO 1994-US10539 19940916; US 1996-597005 19960205.

GI

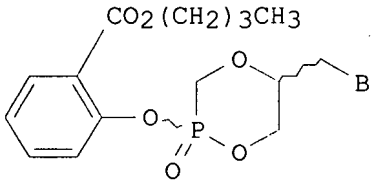


I

AB Nucleotide analogs I (B = nucleobase, L = amidite oxy ester, amidite thio ester) characterized by the presence of an amidate linked amino acid or an ester linked group which is bonded to the phosphorus atom of phosphonate nucleotide analogs are disclosed. The analogs comprise a phosphoramidate or ester bond that is hydrolyzed in vivo to yield a corresponding phosphonate nucleotide analog. Methods and intermediates for the synthesis and use are described. Thus, (R)-9-(2-di-2-ethoxyphenylphosphonylmethoxypropyl)adenine was prepd. and tested for its antiviral HSV-1 and HSV-2 activities (EC50 = 3-200 .mu.M).

REFERENCE 3: 128:167657 Preparation of cyclic nucleotide phosphonate esters as virucides. Arimilli, Murty N.; Jones, Robert J.; Prisbe, Ernest J. (Gilead Sciences, Inc., USA). U.S. US 5717095 A 19980210, 22 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-774240 19961227.

GI



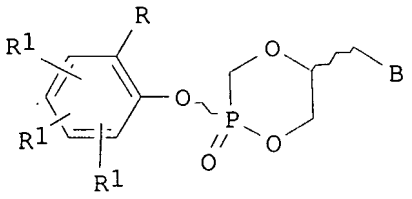
I

AB Cyclic nucleotide phosphonate esters I [B = (un)protected cytosin-1-yl] were prepd. as virucides. Thus, I (B = cytosine) was prepd. and tested for activity against HSV-1 and HSV-2 using MA 104 cells (EC50 = 2-200

.mu.M).

REFERENCE 4: 127:136036 Preparation of nucleotide phosphonate ester analogs as virucides. Arimilli, Murty N.; Bischofberger, Norbert W.; Jones, Robert J.; Lee, William A.; Prisbe, Ernest J. (Gilead Sciences, Inc., USA; Arimilli, Murty N.; Bischofberger, Norbert W.; Jones, Robert J.; Lee, William A.; Prisbe, Ernest J.). PCT Int. Appl. WO 9724361 A1 19970710, 87 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1996-US20226 19961213. PRIORITY: US 1995-581147 19951229; US 1995-9375 19951229; US 1995-9372 19951229.

GI



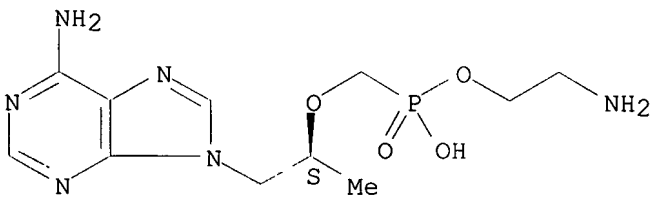
I

AB Nucleotide phosphonate esters I (R = H, alkyl, ether, CHO, CH2Bn, ester, keto, amide, sulfone; R1 = H, CN, NO2, halo, alkyl, ether, ester, keto, SO3H, amine, CHO, OH; B = heterocycle, nucleobase) were prepd. as virucides and immunogens. The analogs comprise an ester bond that is hydrolyzed in vivo to yield a corresponding phosphonate nucleotide analog.

Thus, I (R = R1 = H, B = adenine) was prepd. and tested against HSV-1 and HSV-2. These compds. were tested against HSV-1 and HSV-2 (IC50 = 2-200 .mu.M) compared to 9-(2-Phosphonylmethoxyethyl)adenine (PMEA) (IC50 = 138 .mu.M). Some of these compds. were more active against HSV-2 than PMEA.

L5 ANSWER 21 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 186587-67-7 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, mono(2-aminoethyl) ester, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C11 H19 N6 O4 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



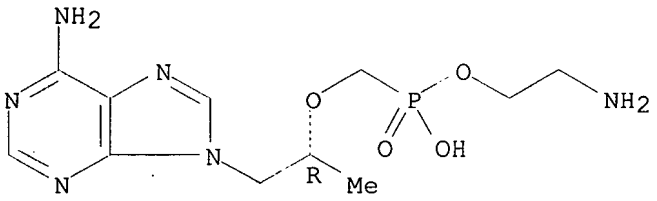
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:144493 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Masojidkova, Milena; Holy, Antonin (Inst. Organic Chem. Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(10), 1538-1548 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765. Publisher: Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic.

AB "Abbreviated" NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties, 9-(2-phosphonomethoxyethyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (RS)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine 2-(3-carbamoyl-pyridinium)ethyl ester, and (S)- and (R)-1-[3-(adenin-9-yl)-2-phosphonatomethoxypropyl]-3-carbamoylpyridinium, were prepd. by multistep syntheses using the Zincke reaction in the last step. The cytostatic activity of title NAD+ analogs was tested on L-1210 mouse leukemia cells. None of the compds. exhibited significant cytostatic activity and neither were cytotoxic. In vitro activities against DNA viruses and retroviruses were detd. (no data).

L5 ANSWER 22 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 186587-66-6 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, mono(2-aminoethyl) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C11 H19 N6 O4 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

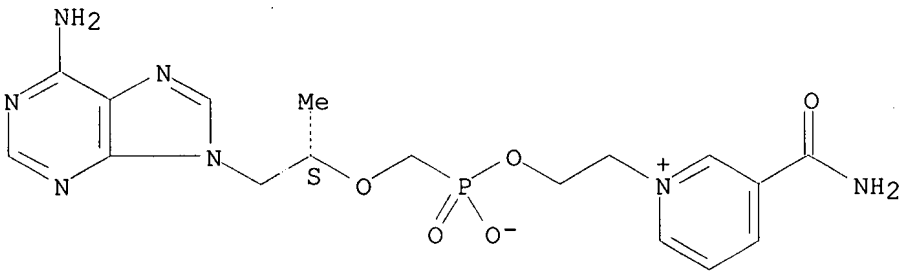
REFERENCE 1: 126:144493 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Masojidkova, Milena; Holy, Antonin (Inst. Organic Chem. Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(10), 1538-1548 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765. Publisher: Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic.

AB "Abbreviated" NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties, 9-(2-phosphonomethoxyethyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (RS)-9-(3-hydroxy-2-

phosphonomethoxypropyl)adenine 2-(3-carbamoyl-pyridinium)ethyl ester, and (S)- and (R)-1-[3-(adenin-9-yl)-2-phosphonatomethoxypropyl]-3-carbamoylpyridinium, were prepd. by multistep syntheses using the Zincke reaction in the last step. The cytostatic activity of title NAD+ analogs was tested on L-1210 mouse leukemia cells. None of the compds. exhibited significant cytostatic activity and neither were cytotoxic. In vitro activities against DNA viruses and retroviruses were detd. (no data).

L5 ANSWER 23 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 183107-11-1 REGISTRY
CN Pyridinium, 3-(aminocarbonyl)-1-[2-[[[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]hydroxyphosphinyl]oxy]ethyl]-, inner salt, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C17 H22 N7 O5 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:144493 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Masojidkova, Milena; Holy, Antonin (Inst. Organic Chem. Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(10), 1538-1548 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765. Publisher: Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic.

AB "Abbreviated" NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties, 9-(2-phosphonomethoxyethyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (RS)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine 2-(3-carbamoyl-pyridinium)ethyl ester, and (S)- and (R)-1-[3-(adenin-9-yl)-2-phosphonatomethoxypropyl]-3-carbamoylpyridinium, were prepd. by multistep syntheses using the Zincke reaction in the last step. The cytostatic activity of title NAD+ analogs was tested on L-1210 mouse leukemia cells. None of the compds. exhibited significant cytostatic activity and neither were cytotoxic. In vitro activities against DNA viruses and retroviruses were detd. (no data).

REFERENCE 2: 125:301463 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S52-S54 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

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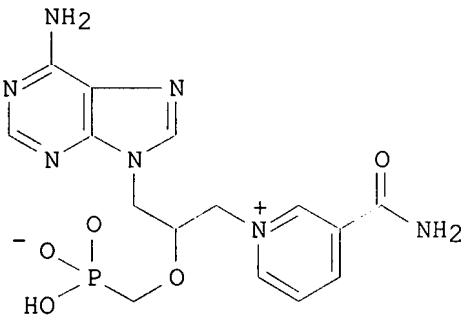

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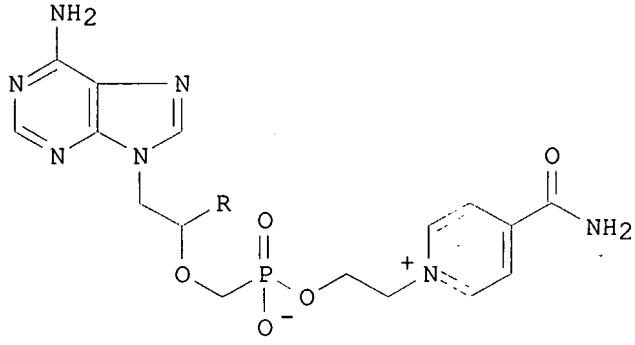
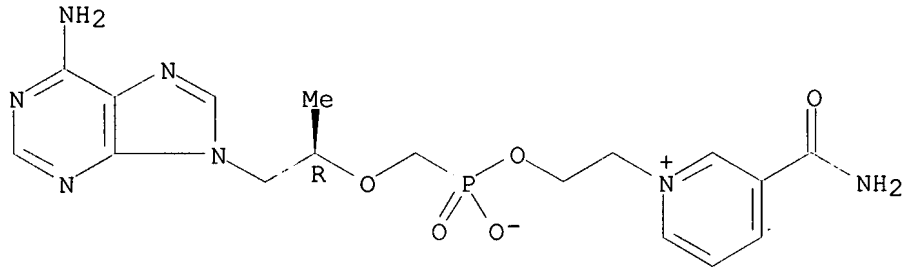


II

AB New types of NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties were prepd. by multistep syntheses using the Zincke reaction as the last step. The structures of the compds. were derived from the biol. active acyclic nucleotide analogs. Example compds. were (R)-I and (S)-I. None of the compds. thus prepd. showed significant co-enzymic activity. However, (R)-I and (S)-I possessed antiviral activity. Also prepd. were the NAD+ analogs II (R = H, Me, etc.).

L5 ANSWER 24 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 183107-10-0 REGISTRY
CN Pyridinium, 3-(aminocarbonyl)-1-[2-[[[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]hydroxyphosphinyl]oxy]ethyl]-, inner salt, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C17 H22 N7 O5 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



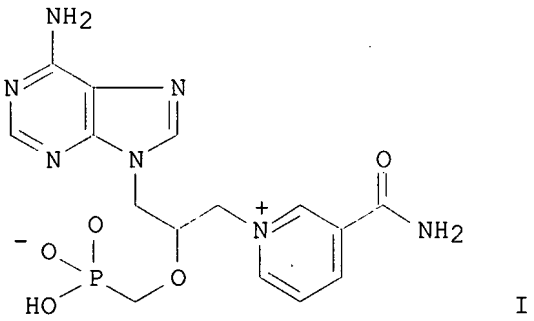
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:144493 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Masojidkova, Milena; Holy, Antonin (Inst. Organic Chem. Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(10), 1538-1548 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765. Publisher: Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic.

AB "Abbreviated" NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties, 9-(2-phosphonomethoxyethyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (RS)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine 2-(3-carbamoyl-pyridinium)ethyl ester, and (S)- and (R)-1-[3-(adenin-9-yl)-2-phosphonatomethoxypropyl]-3-carbamoylpyridinium, were prepd. by multistep syntheses using the Zincke reaction in the last step. The cytostatic activity of title NAD+ analogs was tested on L-1210 mouse leukemia cells. None of the compds. exhibited significant cytostatic activity and neither were cytotoxic. In vitro activities against DNA viruses and retroviruses were detd. (no data).

REFERENCE 2: 125:301463 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S52-S54 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

GI



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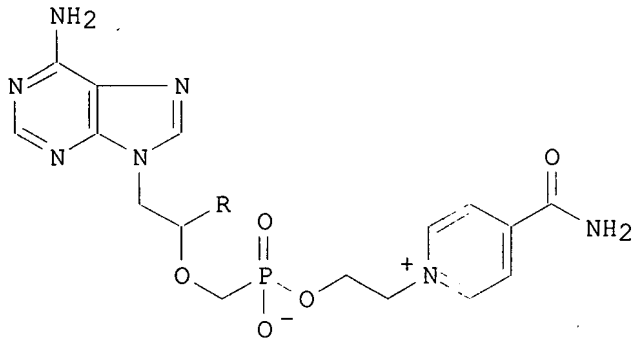
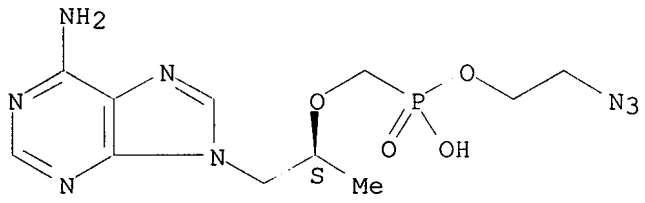


II

AB New types of NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties were prepd. by multistep syntheses using the Zincke reaction as the last step. The structures of the compds. were derived from the biol. active acyclic nucleotide analogs. Example compds. were (R)-I and (S)-I. None of the compds. thus prepd. showed significant co-enzymic activity. However, (R)-I and (S)-I possessed antiviral activity. Also prepd. were the NAD+ analogs II (R = H, Me, etc.).

L5 ANSWER 25 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 183107-04-2 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, mono(2-azidoethyl) ester, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C11 H17 N8 O4 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

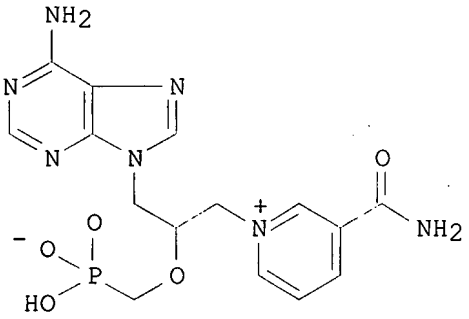
REFERENCE 1: 126:144493 "Abbreviated" NAD+ analogs containing a phosphonate

function. Hockova, Dana; Masojidkova, Milena; Holy, Antonin (Inst. Organic Chem. Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(10), 1538-1548 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765. Publisher: Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic.

AB "Abbreviated" NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties, 9-(2-phosphonomethoxyethyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (RS)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine 2-(3-carbamoyl-pyridinium)ethyl ester, and (S)- and (R)-1-[3-(adenin-9-yl)-2-phosphonatomethoxypropyl]-3-carbamoylpyridinium, were prepd. by multistep syntheses using the Zincke reaction in the last step. The cytostatic activity of title NAD+ analogs was tested on L-1210 mouse leukemia cells. None of the compds. exhibited significant cytostatic activity and neither were cytotoxic. In vitro activities against DNA viruses and retroviruses were detd. (no data).

REFERENCE 2: 125:301463 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S52-S54 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

GI



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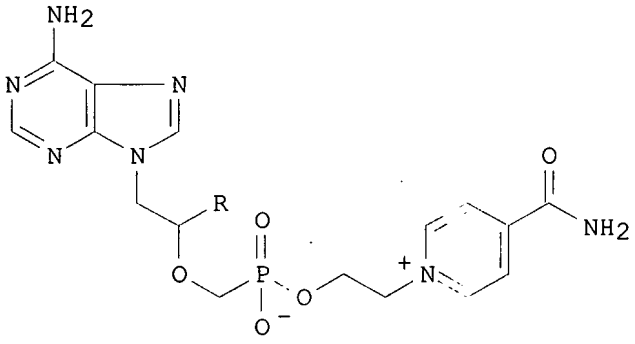


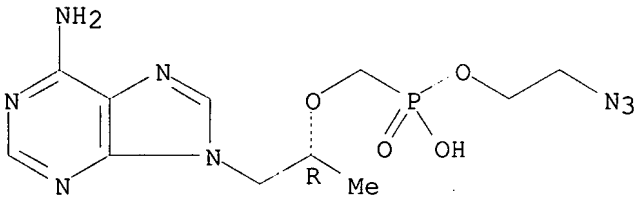
II

AB New types of NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties were prepd. by multistep syntheses using the Zincke reaction as the last step. The structures of the compds. were derived from the biol. active acyclic

nucleotide analogs. Example compds. were (R)-I and (S)-I. None of the compds. thus prepd. showed significant co-enzymic activity. However, (R)-I and (S)-I possessed antiviral activity. Also prepd. were the NAD+ analogs II (R = H, Me, etc.).

L5 ANSWER 26 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 183107-03-1 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, mono(2-azidoethyl) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C11 H17 N8 O4 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



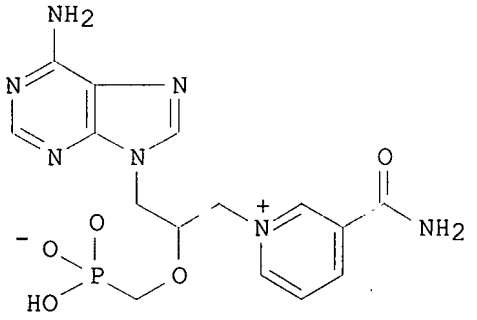
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 126:144493 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Masojidkova, Milena; Holy, Antonin (Inst. Organic Chem. Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(10), 1538-1548 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765. Publisher: Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic.

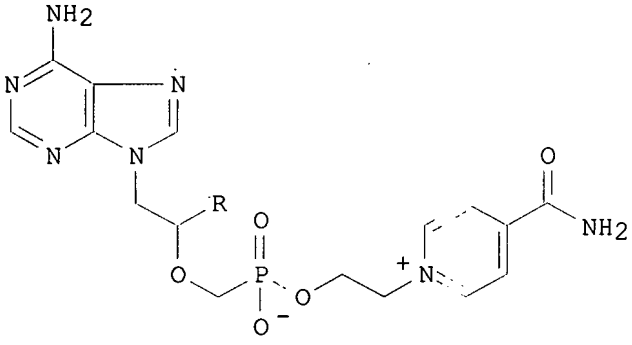
AB "Abbreviated" NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties, 9-(2-phosphonomethoxyethyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (RS)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine 2-(3-carbamoyl-pyridinium)ethyl ester, and (S)- and (R)-1-[3-(adenin-9-yl)-2-phosphonatomethoxypropyl]-3-carbamoylpyridinium, were prepd. by multistep syntheses using the Zincke reaction in the last step. The cytostatic activity of title NAD+ analogs was tested on L-1210 mouse leukemia cells. None of the compds. exhibited significant cytostatic activity and neither were cytotoxic. In vitro activities against DNA viruses and retroviruses were detd. (no data).

REFERENCE 2: 125:301463 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S52-S54 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

GI



I

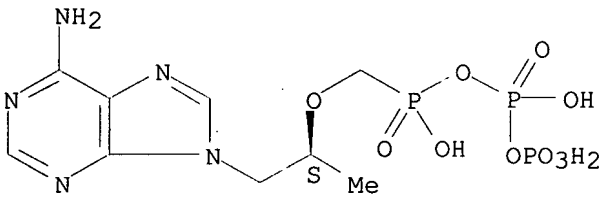


II

AB New types of NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties were prepd. by multistep syntheses using the Zincke reaction as the last step. The structures of the compds. were derived from the biol. active acyclic nucleotide analogs. Example compds. were (R)-I and (S)-I. None of the compds. thus prepd. showed significant co-enzymic activity. However, (R)-I and (S)-I possessed antiviral activity. Also prepd. were the NAD+ analogs II (R = H, Me, etc.).

L5 ANSWER 27 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 182415-40-3 REGISTRY
CN Diphosphoric acid, monoanhydride with [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C9 H16 N5 O10 P3
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

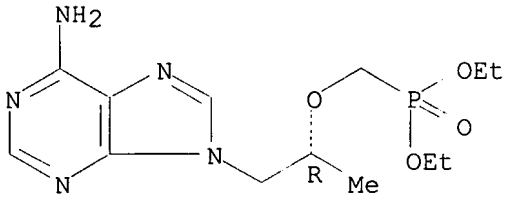
REFERENCE 1: 125:268990 Structural features of acyclic nucleotide analogs

conferring inhibitory effects on cellular replicative DNA polymerases. Kramata, Pavel; Birkus, Gabriel; Otmar, Miroslav; Votruba, Ivan; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S188-S191 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

AB Diphosphates of phosphonomethoxyalkyl acyclic nucleotide analogs were tested as inhibitors of two proteolyzed forms of cellular repetitive DNA polymerase .epsilon., and DNA polymerases .alpha. and .delta.. The Ki/Km ratios are given. Effects of different substitutions on their inhibitory activity are discussed.

L5 ANSWER 28 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 180587-75-1 REGISTRY
CN Phosphonic acid, [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, diethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, diethyl ester, (R)-
FS STEREOSEARCH
MF C13 H22 N5 O4 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry. Rotation (-).



5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:158419 Antiviral nucleotide analog composition and synthesis method. Munger, John D., Jr.; Rohloff, John C.; Schultze, Lisa M. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9905150 A1 19990204, 43 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US15254 19980723. PRIORITY: US 1997-900752 19970725; US 1997-53777 19970725.

AB The invention provides a compn. comprising 9-[2-(R)-[[Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]adenine [bis(POC)PMPA] and fumaric acid (1:1) for oral delivery of (R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA). The compn. is useful as an intermediate for the prepn. of antiviral compds., or is useful for administration to patients for antiviral therapy or prophylaxis. The compn. is particularly useful when administered orally. The invention also provides methods to make PMPA and intermediates in PMPA synthesis.

Embodiments include lithium t-butoxide, 9-(2-hydroxypropyl)adenine and di-Et p-toluenesulfonylmethoxy-phosphonate in an org. solvent such as DMF.

The reaction results in di-Et PMPA prepns. contg. an improved byproduct profile compared to di-Et PMPA made by prior methods. "Bis(POC)PMPA" fumarate, or BPPF, was prepd. in 7 steps via reaction of (R)-4-methyl-1,3-dioxolan-2-one with adenine and etherification of the product with (EtO)2P(O)CH2-OTs.

REFERENCE 2: 128:286431 PMPA preparation [for pharmaceutical use]. Bischofberger, Norbert W. (Gilead Sciences, Inc., USA). U.S. US 5733788 A 19980331, 7 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-686829 19960726.

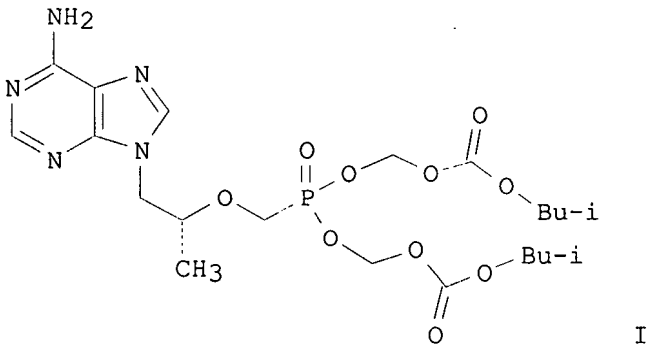
AB PMPA [(R)-9-[2-(phosphonomethoxy)propyl]adenine] compns. are purified to >95% by removing undesired contaminants such as bisPMPA adduct, adenine, hydroxypropyladenine and propenyladenine. These purified PMPA compns. are useful in pharmaceuticals for the treatment or prophylaxis of viral infections.

REFERENCE 3: 128:270818 Practical synthesis of the anti-HIV drug, PMPA. Schultze, Lisa M.; Chapman, Harlan H.; Dubree, Nathan J. P.; Jones, Robert J.; Kent, Kenneth M.; Lee, Thomas T.; Louie, Michael S.; Postich, Michael J.; Prisbe, Ernest J.; Rohloff, John C.; Yu, Richard H. (Process Chemistry and Analytical Chemistry, Gilead Sciences, Foster City, CA, 94404, USA). Tetrahedron Lett., 39(14), 1853-1856 (English) 1998. CODEN: TELEAY. ISSN: 0040-4039. Publisher: Elsevier Science Ltd..

AB The anti-HIV nucleotide analog PMPA can be prepd. on a kilogram-scale by a three step sequence: i) condensation of adenine with (R)-propylene carbonate, ii) alkylation of the resulting (R)-9-(2-hydroxypropyl)adenine with di-Et p-toluenesulfonyloxymethanephosphonate using lithium tert-butoxide and iii) cleavage of the phosphonate ester functionalities with bromotrimethylsilane.

REFERENCE 4: 128:140970 Preparation of phosphonomethoxy acyclic nucleotide analogs as antiviral agents. Arimilli, Murty N.; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

GI



I

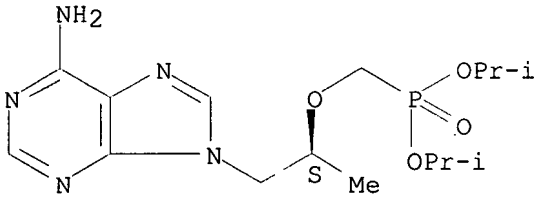
AB Compds. are provided that comprise esters of antiviral phosphonomethoxy nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn. of antiviral compds. or oligonucleotides, or are useful for administration directly to patients for antiviral therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

REFERENCE 5: 125:194962 Kinetic Resolution of Terminal Epoxides via Highly Regioselective and Enantioselective Ring Opening with TMSN3. An Efficient, Catalytic Route to 1,2-Amino Alcohols. Larrow, Jay F.; Schaus, Scott E.; Jacobsen, Eric N. (Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA, 02138, USA). J. Am. Chem. Soc., 118(31), 7420-7421 (English) 1996. CODEN: JACSAT. ISSN: 0002-7863.

AB The (salen)Cr-catalyzed asym. epoxide ring opening reaction has been applied to the kinetic resoln. of racemic terminal epoxides to provide 1-azido-2-trimethylsiloxyalkanes in 89-98% enantiomeric excess. The products are obtained in high yields and in excellent, often abs., regiochem. purity. Epoxides bearing unbranched alkyl substituents were found to undergo kinetic resoln. with highest efficiency, with krel values well in excess of 100 for these substrates. The reaction also showed good functional group compatibility, with epoxides bearing chloride, alkoxide, and even Lewis basic cyano substituents displaying clean and highly enantioselective reactions. The utility of the ring-opened products as precursors to 1,2-amino alcs. was demonstrated by the synthesis of (S)-propranolol, a well-known antihypertensive agent, and of (R)-9-[2-(phosphonomethoxy)propyl]adenine, a compd. recently shown to display prophylactic activity against SIV infection.

L5 ANSWER 29 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 173277-57-1 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H26 N5 O4 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry. Rotation (+).



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:146698 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. II. The synthon approach. Holy, Antonin; Dvorakova, Hana; Masojidkova, Milena
(Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(8), 1390-409 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.
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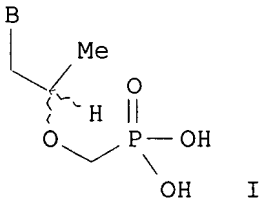
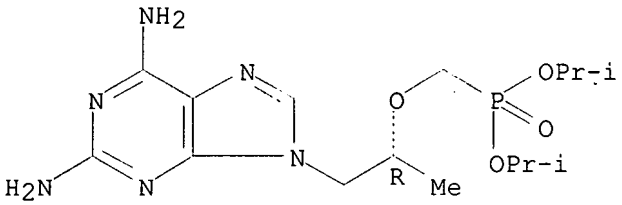


AB Acyclic nucleotides, e.g. I (B = adenine, guanine, hypoxanthine), were prepd. from the corresponding 1-benzyloxy-2-propanol.

L5 ANSWER 30 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 173277-53-7 REGISTRY
CN Phosphonic acid, [[2-(2,6-diamino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H27 N6 O4 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry. Rotation (-).



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:146698 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. II. The synthon approach. Holy, Antonin; Dvorakova, Hana; Masojidkova, Milena
(Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(8), 1390-409 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.

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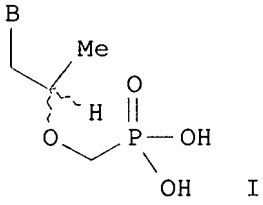
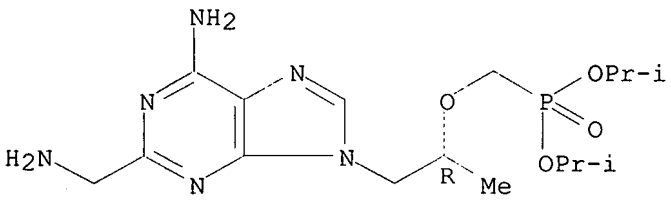


I

AB Acyclic nucleotides, e.g. I (B = adenine, guanine, hypoxanthine), were prepd. from the corresponding 1-benzyloxy-2-propanol.

L5 ANSWER 31 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 170874-70-1 REGISTRY
CN Phosphonic acid, [[2-[6-amino-2-(aminomethyl)-9H-purin-9-yl]-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C16 H29 N6 O4 P
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

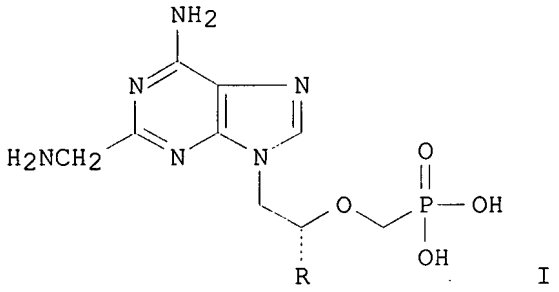


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9276 Synthesis of acyclic nucleotide analogs derived from

2-(aminomethyl)adenine and 2-(aminomethyl)hypoxanthine. Hocek, Michal; Masojidkova, Milena; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(5), 875-82 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.

GI



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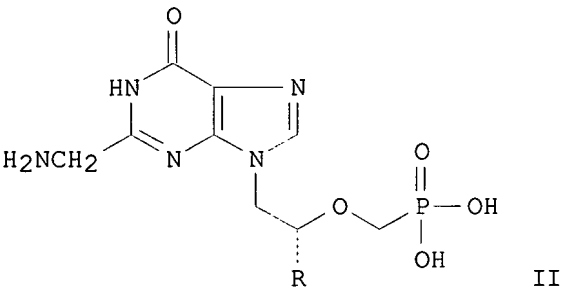
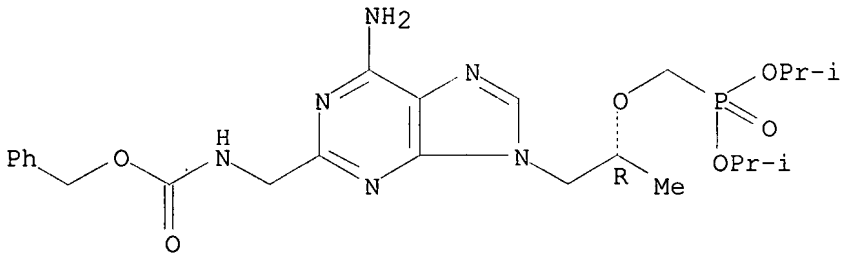


II

AB Synthesis of a series of 2-(aminomethyl)-9-(2-phosphonomethoxyalkyl)adenines I (R = H, Me, CH2OH) and hypoxanthines II (R = H, Me, CH2OH) is reported. None of I and II showed any significant antiviral or cytostatic activity, nor did it exhibit any considerable cell toxicity.

L5 ANSWER 32 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 170874-61-0 REGISTRY
CN Carbamic acid, [[6-amino-9-[2-[[bis(1-methylethoxy)phosphinyl]methoxy]propyl]-9H-purin-2-yl]methyl]-, phenylmethyl ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H35 N6 O6 P
SR CA
LC STN Files: CA, CAPLUS

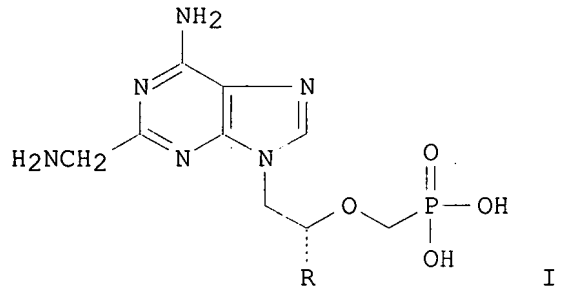
Absolute stereochemistry.



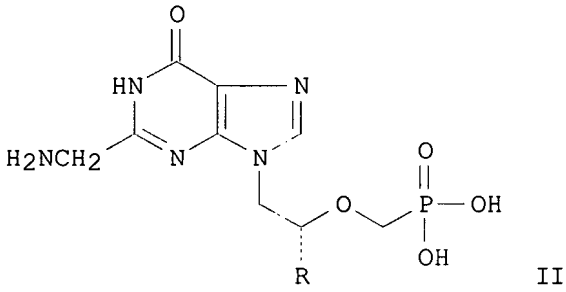
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:9276 Synthesis of acyclic nucleotide analogs derived from 2-(aminomethyl)adenine and 2-(aminomethyl)hypoxanthine. Hocek, Michal; Masojidkova, Milena; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(5), 875-82 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.

GI



I



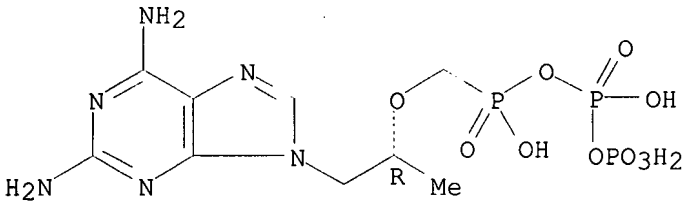
II

AB Synthesis of a series of 2-(aminomethyl)-9-(2-phosphonomethoxyalkyl)adenines I (R = H, Me, CH2OH) and hypoxanthines II (R = H, Me, CH2OH) is reported. None of I and II showed any significant antiviral or cytostatic activity, nor did it exhibit any considerable cell toxicity.

L5 ANSWER 33 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 166403-67-4 REGISTRY
CN Diphosphoric acid, monoanhydride with [[2-(2,6-diamino-9H-purin-9-yl)-1-

methylethoxy]methyl]phosphonic acid, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C9 H17 N6 O10 P3
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:44484 Incorporation of selected nucleoside phosphonates and anti-human immunodeficiency virus nucleotide analogs into DNA by human DNA polymerases .alpha., .beta. and .gamma.. Cihlar, T.; Chen, M. S. (Gilead Sciences, Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 8(3), 187-195 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB Incorporation of selected diphosphates of nucleoside phosphonates and triphosphates of currently approved anti-human immunodeficiency virus nucleoside analogs into DNA by human DNA polymerases .alpha., .beta. and .gamma. was studied. All three polymerases were able to incorporate diphosphates of 9-(2-phosphonomethoxyethyl)adenine (PMEApp), 9-(2-phosphonomethoxyethyl)guanine (PMEGpp), (R)-9-(2-phosphonomethoxypropyl)adenine (PMPApp), (R)-9-(2-phosphononomethoxypropyl)-2,6-diaminopurine (PMPDAPpp) and (2R,5R)-9-[2,5-dihydro-5-(phosphonomethoxy)-2-furanyl]adenine (D4APpp) into primer/template DNA of defined sequence. After incorporation, these nucleoside phosphonates acted as terminators of primer extension. Kinetic consts. of their incorporation were detd. and compared with those for incorporation of ddATP, ddCTP, (-)-2'-deoxy-3'-thiacytidine triphosphate (3TC-TP), 2',3'-didehydro-3'-deoxythymidine triphosphate (d4T-TP) and 3'-azido-3'-deoxythymidine triphosphate (AZT-TP). Relative efficiencies of incorporation (percentage of the incorporation efficiency for the corresponding natural deoxynucleoside triphosphate) by DNA polymerase .alpha. ranged from 0.05% for 3TC-TP to 51% for PMEGpp. DNA polymerase .beta. catalyzed the incorporation with relative efficiencies ranging from 0.014% for AZT-TP to 125% for ddCTP, and efficiencies of incorporation by DNA polymerase .gamma. varied between 0.13% for 3TC-TP and 325% for ddCTP. Generally, the lowest incorporation efficiencies with all three polymerases were found for PMPApp (0.06-1.4%) and PMPDAPpp (0.075-2.2%).

REFERENCE 2: 125:268990 Structural features of acyclic nucleotide analogs conferring inhibitory effects on cellular replicative DNA polymerases. Kramata, Pavel; Birkus, Gabriel; Otmar, Miroslav; Votruba, Ivan; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun.,

61(Spec. Issue), S188-S191 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

AB Diphosphates of phosphonomethoxyalkyl acyclic nucleotide analogs were tested as inhibitors of two proteolyzed forms of cellular repetitive DNA polymerase .epsilon., and DNA polymerases .alpha. and .delta.. The Ki/Km ratios are given. Effects of different substitutions on their inhibitory activity are discussed.

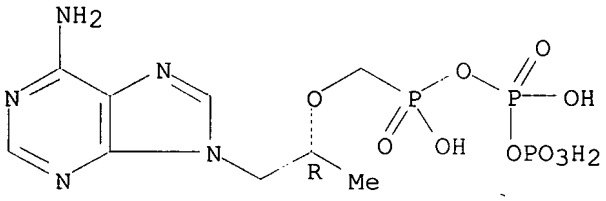
REFERENCE 3: 123:136923 Kinetic interaction of the diphosphates of 9-(2-phosphonylmethoxyethyl)adenine and other anti-HIV active purine congeners with HIV reverse transcriptase and human DNA polymerases .alpha., .beta. and .gamma.. Cherrington, J. M.; Allen, S. J. W.; Bischofberger, N.; Chen, M. S. (Gilead Sciences, Inc., Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 6(4), 217-21 (English) 1995. CODEN: ACCHEH. ISSN: 0956-3202.

AB The inhibitory effects of the diphosphates of 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and its analogs on HIV reverse transcriptase and human DNA polymerases .alpha., .beta., and .gamma. were studied. The analogs investigated were the diphosphates of 9-(2-phosphonylmethoxypropyl)adenine (PMPApp), 9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine (PMPDAPpp), and (2R,5R)-9-[2,5-dihydro-5-(phosphonylmethoxy)-2-furanyl]adenine (D4APpp). These 4 compds. were much more inhibitory to HIV reverse transcriptase when an RNA template rather than a DNA template was used. The Ki values for the 4 compds. were in the range of 11-22 nM with an RNA template. The Ki values for ddCTP and AZTTP were 54 and 8 nM, resp. PMEApp and its analogs showed varying degrees of inhibition of the human DNA polymerases.

The Ki values for PMEApp, PMPApp and PMPDAPpp against DNA polymerase .alpha. were in the micromolar range, whereas D4APpp was a poor inhibitor of this enzyme with a Ki of 65.9 .mu.M. The inhibition of DNA polymerase .beta. by PMEApp, PMPApp and D4Appp was minimal, whereas PMPDAPpp showed higher inhibition of DNA polymerase .beta. with a Ki of 9.71 .mu.M. The Ki values for PMEApp and D4APpp against DNA polymerase .gamma. were submicromolar, whereas PMPApp and PMPDAPpp were much less inhibitory to this enzyme. For comparison, ddCTP was found to be a more potent inhibitor of DNA polymerases .beta. and .gamma. than the diphosphates of PMEA and its analogs.

L5 ANSWER 34 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 166403-66-3 REGISTRY
CN Diphosphoric acid, monoanhydride with [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphonic acid, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C9 H16 N5 O10 P3
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)

3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 127:44484 Incorporation of selected nucleoside phosphonates and anti-human immunodeficiency virus nucleotide analogs into DNA by human DNA polymerases .alpha., .beta. and .gamma.. Cihlar, T.; Chen, M. S. (Gilead Sciences, Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 8(3), 187-195 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB Incorporation of selected diphosphates of nucleoside phosphonates and triphosphates of currently approved anti-human immunodeficiency virus nucleoside analogs into DNA by human DNA polymerases .alpha., .beta. and .gamma. was studied. All three polymerases were able to incorporate diphosphates of 9-(2-phosphonomethoxyethyl)adenine (PMEApp), 9-(2-phosphonomethoxyethyl)guanine (PMEGpp), (R)-9-(2-phosphonomethoxypropyl)adenine (PMPApp), (R)-9-(2-phosphononomethoxypropyl)-2,6-diaminopurine (PMPDAPpp) and (2R,5R)-9-[2,5-dihydro-5-(phosphonomethoxy)-2-furanyl]adenine (D4APpp) into primer/template DNA of defined sequence. After incorporation, these nucleoside phosphonates acted as terminators of primer extension. Kinetic consts. of their incorporation were detd. and compared with those for incorporation of ddATP, ddCTP, (-)-2'-deoxy-3'-thiacytidine triphosphate (3TC-TP), 2',3'-didehydro-3'-deoxythymidine triphosphate (d4T-TP) and 3'-azido-3'-deoxythymidine triphosphate (AZT-TP). Relative efficiencies of incorporation (percentage of the incorporation efficiency for the corresponding natural deoxynucleoside triphosphate) by DNA polymerase .alpha. ranged from 0.05% for 3TC-TP to 51% for PMEGpp. DNA polymerase .beta. catalyzed the incorporation with relative efficiencies ranging from 0.014% for AZT-TP to 125% for ddCTP, and efficiencies of incorporation by DNA polymerase .gamma. varied between 0.13% for 3TC-TP and 325% for ddCTP. Generally, the lowest incorporation efficiencies with all three polymerases were found for PMPApp (0.06-1.4%) and PMPDAPpp (0.075-2.2%).

REFERENCE 2: 125:268990 Structural features of acyclic nucleotide analogs conferring inhibitory effects on cellular replicative DNA polymerases. Kramata, Pavel; Birkus, Gabriel; Otmar, Miroslav; Votruba, Ivan; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S188-S191 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

AB Diphosphates of phosphonomethoxyalkyl acyclic nucleotide analogs were tested as inhibitors of two proteolyzed forms of cellular repetitive DNA polymerase .epsilon., and DNA polymerases .alpha. and .delta.. The Ki/Km ratios are given. Effects of different substitutions on their inhibitory activity are discussed.

REFERENCE 3: 123:136923 Kinetic interaction of the diphosphates of 9-(2-phosphonylmethoxyethyl)adenine and other anti-HIV active purine congeners with HIV reverse transcriptase and human DNA polymerases .alpha., .beta. and .gamma.. Cherrington, J. M.; Allen, S. J. W.; Bischofberger, N.; Chen, M. S. (Gilead Sciences, Inc., Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 6(4), 217-21 (English) 1995. CODEN: ACCHEH. ISSN: 0956-3202.

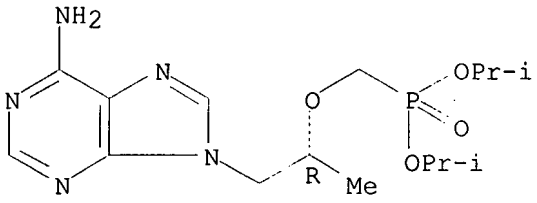
AB The inhibitory effects of the diphosphates of 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and its analogs on HIV reverse transcriptase and human DNA polymerases .alpha., .beta., and .gamma. were

studied. The analogs investigated were the diphosphates of 9-(2-phosphonylmethoxypropyl)adenine (PMPApp), 9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine (PMPDAPpp), and (2R,5R)-9-[2,5-dihydro-5-(phosphonylmethoxy)-2-furanyl]adenine (D4APpp). These 4 compds. were much more inhibitory to HIV reverse transcriptase when an RNA template rather than a DNA template was used. The Ki values for the 4 compds. were in the range of 11-22 nM with an RNA template. The Ki values for ddCTP and AZTTP were 54 and 8 nM, resp. PMEApp and its analogs showed varying degrees of inhibition of the human DNA polymerases.

The Ki values for PMEApp, PMPApp and PMPDAPpp against DNA polymerase .alpha. were in the micromolar range, whereas D4APpp was a poor inhibitor of this enzyme with a Ki of 65.9 .mu.M. The inhibition of DNA polymerase .beta. by PMEApp, PMPApp and D4Appp was minimal, whereas PMPDAPpp showed higher inhibition of DNA polymerase .beta. with a Ki of 9.71 .mu.M. The Ki values for PMEApp and D4APpp against DNA polymerase .gamma. were submicromolar, whereas PMPApp and PMPDAPpp were much less inhibitory to this enzyme. For comparison, ddCTP was found to be a more potent inhibitor of DNA polymerases .beta. and .gamma. than the diphosphates of PMEA and its analogs.

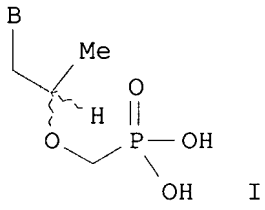
L5 ANSWER 35 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 160616-04-6 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, bis(1-methylethyl) ester, (R)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C15 H26 N5 O4 P
SR CA
LC STN Files: CA, CAPLUS, CASREACT

Absolute stereochemistry.



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

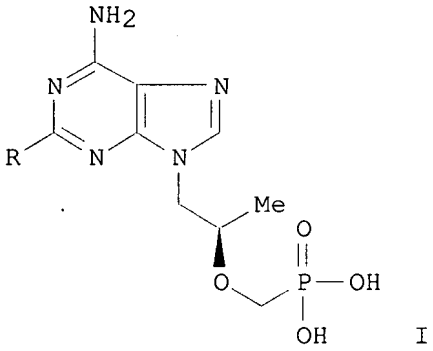
REFERENCE 1: 124:146698 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. II. The synthon approach. Holy, Antonin; Dvorakova, Hana; Masojidkova, Milena
(Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(8), 1390-409 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.
GI



I

AB Acyclic nucleotides, e.g. I (B = adenine, guanine, hypoxanthine), were prepd. from the corresponding 1-benzyloxy-2-propanol.

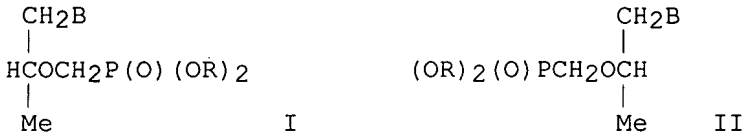
REFERENCE 2: 124:117829 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. I. The stepwise approach. Holy, Antonin; Masojidkova, Milena (Inst. Org. Chem. Biochem., Acad. Sci., Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(7), 1196-212 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.
GI



I

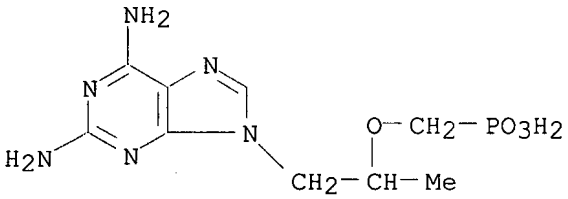
AB Phosphonomethoxypropyl acyclic nucleotide analogs, e.g. I (R = H, NH2), were prepd. via alkylation of N-protected N-(2-hydroxypropyl) derivs. of the corresponding bases with bis(2-propyl) p-toluenesulfonyloxymethylphosphonate. This approach was used for the synthesis of cytosine, adenine and 2,6-diaminopurine derivs., while compds. derived from guanine were prepd. by hydrolysis of 2-amino-6-chloropurine intermediates.

REFERENCE 3: 122:106401 preparation of antiretroviral enantiomeric nucleotide analogs. Holy, Antonin; Dvorakova, Hana; Declercq, Erik Desire Alice; Balzarini, Jan Marie Rene (Institute of Organic Chemistry and Biochemistry, Czech Rep.; Rega Stichting V.Z.W.; Gilead Sciences, Inc.). PCT Int. Appl. WO 9403467 A2 19940217, 96 pp. DESIGNATED STATES: W: CA, CZ, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US7360 19930804.
PRIORITY: US 1992-925610 19920805.
GI



AB Resolved enantiomers of formulas I and II [B is a purine or pyrimidine base; R = H, C1-6 alkyl, aryl, aralkyl] or their aza and/or deaza analogs, useful in antiviral pharmaceutical compns. to treat retroviral infections, are prepd. via hydrolysis of the appropriate phosphate ester. E.g., iso-Bu (R)-lactate was protected with 3,4-dihydro-2H-pyran, the resulting iso-Bu (R)-2-O-(tetrahydropyranyl)lactate was reduced with LiAlH4, the resulting 2-O-(tetrahydropyranyl)-(R)-propane-1,2-diol was 1-O-tosylated, the resulting 1-O-tosyl-2-O-(tetrahydropyranyl)propane-1,2-diol was reacted with adenine in DMF contg. cesium carbonate and the product was deprotected, the resulting 9-(R)-(2-hydroxypropyl)adenine was first N6-benzoylated and the product was treated with diisopropyl (p-toluenesulfonyloxy)methylphosphonate in DMF contg. NaH, the product was deprotected at the N6 position with MeONa-MeOH followed by hydrolysis to give (2'R)-I [B = 9-adeninyl, R = isopropyl]. In an in vitro study this had an EC50 of 1.7 and 1.4 .mu.g/Ml, resp., against HIV-1- and HIV-2-induced cytopathicity in human lymphocyte MT-4 cells.

L5 ANSWER 36 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 156644-97-2 REGISTRY
CN Phosphonic acid, [[2-(2,6-diamino-9H-purin-9-yl)-1-methylethoxy]methyl]- (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C9 H15 N6 O4 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



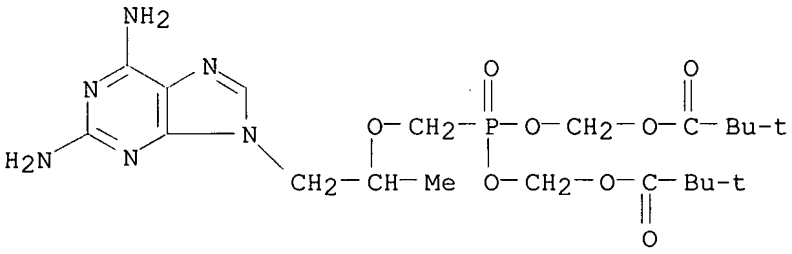
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:73257 Susceptibilities of zidovudine-resistant variants of human immunodeficiency virus type 1 to inhibition by acyclic nucleoside phosphonates. Gong, Yi Fei; Marshall, Dana R.; Srinivas, Ranga V.; Fridland, Arnold (Dep. Infect. Dis., St. Jude Children's Hosp., Memphis, TN, 38101, USA). Antimicrob. Agents Chemother., 38(7), 1683-7 (English) 1994. CODEN: AMACCQ. ISSN: 0066-4804.

AB The acyclic purine nucleoside phosphonates, a newly described class of broad-spectrum antiviral agents, effectively inhibit human immunodeficiency virus type 1 (HIV-1) replication in vitro and in animal

AIDS models. 9-(2-Phosphonylmethoxyethyl)adenine (PMEA) is currently being evaluated in clin. trials in patients with AIDS. In this study, the authors investigated the efficacy of PMEA and a related analog, 9-(2-phosphonylmethoxypropyl)diaminopurine (PMPDAP), against HIV-1 isolates exhibiting various degrees of resistance to zidovudine (azidothymidine, AZT). HIV isolates highly (.apprx.50 to 200-fold) resistant to AZT were about two- to eightfold less susceptible to PMEA. A comparable degree of cross-resistance to PMPDAP, a structurally related analog of PMEA, was also obsd. However, the 50% ED values of PMEA or PMPDAP against a panel of HIV isolates showing intermediate levels (.apprx.8 to 25-fold) of AZT resistance was indistinguishable from the 50% ED values of PMEA (0.7 to 1.7 vs. 2 .mu.M) or PMPDAP (0.4 to 1.4 vs. 0.8 to 1 .mu.M) against HIV isolates from patients who had not previously used AZT. In addn., the authors were unable to generate PMEA- (or PMPDAP)-resistant HIV-1 variants by >30 serial passages of the virus in the presence of increasing concns. of PMEA. Careful anal. of HIV-1 isolates from patients previously treated with AZT for cross-resistance to PMEA are needed to evaluate the significance of these observations.

L5 ANSWER 37 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 151778-87-9 REGISTRY
CN Propanoic acid, 2,2-dimethyl-, [[[2-(2,6-diamino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C21 H35 N6 O8 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

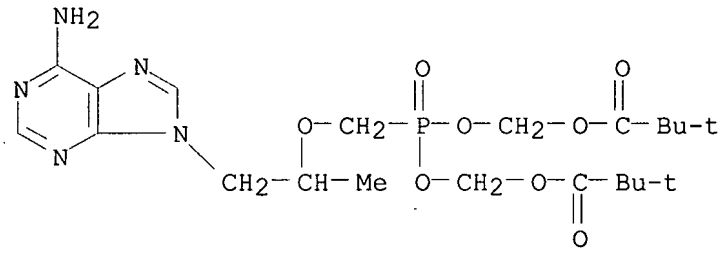


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:170 Metabolism and in vitro antiretroviral activities of bis(pivaloyloxymethyl) prodrugs of acyclic nucleoside phosphonates. Srinivas, R. V.; Robbins, B. L.; Connelly, M. C.; Gong, Y. F.; Bischofberger, N.; Fridland, A. (Dep. Infect. Dis., St. Jude Child. Res. Hosp., Memphis, TN, 38101, USA). Antimicrob. Agents Chemother., 37(10), 2247-50 (English) 1993. CODEN: AMACCQ. ISSN: 0066-4804.
AB Bis(pivaloyloxymethyl) [bis(pom)] esters of the acyclic nucleoside phosphonates 9-(2-phosphonylmethoxyethyl)adenine (PMEA), 9-(2-phosphonylmethoxypropyl)adenine, and 9-(2-phosphonylmethoxypropyl)diaminopurine exhibited 9-23-fold greater antiviral activity (against HIV-1) than their corresponding unmodified compds. The cytotoxicity of the bis(pom) analogs to the host MT-2 cells

was also increased by various degrees, thus altering the therapeutic indexes of these compds. Metabolic studies using [3H]bis(pom)PMEA and [3H]PMEA as model compds. suggested a >100-fold increase in the cellular uptake of the bis(pom) deriv. and formation of active diphosphorylated metabolite. However, the bis(pom) derivs. were chem. unstable and highly susceptible to serum-mediated hydrolysis, factors which limit their potential utility for intracellular drug delivery.

L5 ANSWER 38 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 151778-86-8 REGISTRY
CN Propanoic acid, 2,2-dimethyl-, [[[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]phosphinylidene]bis(oxymethylene) ester (9CI) (CA INDEX NAME)
FS 3D CONCORD
MF C21 H34 N5 O8 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



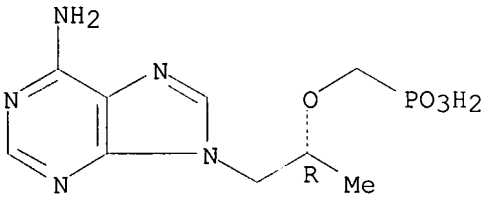
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 120:170 Metabolism and in vitro antiretroviral activities of bis(pivaloyloxymethyl) prodrugs of acyclic nucleoside phosphonates. Srinivas, R. V.; Robbins, B. L.; Connelly, M. C.; Gong, Y. F.; Bischofberger, N.; Fridland, A. (Dep. Infect. Dis., St. Jude Child. Res. Hosp., Memphis, TN, 38101, USA). Antimicrob. Agents Chemother., 37(10), 2247-50 (English) 1993. CODEN: AMACCQ. ISSN: 0066-4804.
AB Bis(pivaloyloxymethyl) [bis(pom)] esters of the acyclic nucleoside phosphonates 9-(2-phosphonylmethoxyethyl)adenine (PMEA), 9-(2-phosphonylmethoxypropyl)adenine, and 9-(2-phosphonylmethoxypropyl)diaminopurine exhibited 9-23-fold greater antiviral activity (against HIV-1) than their corresponding unmodified compds. The cytotoxicity of the bis(pom) analogs to the host MT-2 cells was also increased by various degrees, thus altering the therapeutic indexes of these compds. Metabolic studies using [3H]bis(pom)PMEA and [3H]PMEA as model compds. suggested a >100-fold increase in the cellular uptake of the bis(pom) deriv. and formation of active diphosphorylated metabolite. However, the bis(pom) derivs. were chem. unstable and highly susceptible to serum-mediated hydrolysis, factors which limit their potential utility for intracellular drug delivery.

L5 ANSWER 39 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 147127-20-6 REGISTRY
CN Phosphonic acid, [[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, (R)-
OTHER NAMES:

CN (R)-9-(2-Phosphonomethoxypropyl)adenine
FS STEREOSEARCH
MF C9 H14 N5 O4 P
CI COM
SR CA
LC STN Files: ADISINSIGHT, BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, DRUGUPDATES, IPA, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



57 REFERENCES IN FILE CA (1967 TO DATE)
57 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:82591 Administration of 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) to gravid and infant rhesus macaques (Macaca mulatta): safety and efficacy studies. Tarantal, Alice F.; Marthas, Marta L.; Shaw, Jing-Ping; Cundy, Ken; Bischofberger, Norbert
(California Regional Primate Research Center, University of California, Davis, CA, USA). J. Acquired Immune Defic. Syndr. Hum. Retrovirol., 20(4), 323-333 (English) 1999. CODEN: JDSRET. ISSN: 1077-9450. Publisher: Lippincott Williams & Wilkins.

AB 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) significantly inhibits viral reverse transcription and has been reported to sustain low virus load in SIV-infected rhesus monkeys. Based on these findings, studies were conducted to assess the safety, efficacy, and placental transfer of PMPA when administered once daily s.c. to gravid rhesus monkeys during the second and third trimesters and their offspring (30 mg/kg/day). Fetuses (SIV-infected, N = 6; noninfected, N = 6) were monitored sonog., and maternal/fetal blood samples were collected at select time points for hematol., clin. chem., virol., immunol., and pharmacol. assessments. Newborns were delivered by cesarean section at term and nursery reared for postnatal studies. Infants were administered PMPA once daily beginning on day 2 of life until 9 mo postnatal age. Results of these studies have shown significant placental transport of PMPA, with peak fetal levels at 1 to 3 h post-maternal administration; a significant and sustained redn. in viral load in SIV-infected fetuses and infants; and marked improvements in outcome (e.g., survival, growth, health) in SIV-infected offspring. However, decreased infant body wts. and alterations of select serum biochem. parameters (e.g., decreased phosphorus levels, elevated alk. phosphatase) have been shown to occur in .apprx.67% of PMPA-treated infants, with severe growth restriction and bone-related toxicity in .apprx.25% of animals studied. These data suggest that although PMPA holds great promise for HIV-infected patients, there is the potential for bone-related toxicity at chronic, high dosages, particularly in infants.

REFERENCE 2: 131:39274 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) therapy prolongs survival of infant macaques inoculated with simian immunodeficiency virus with reduced susceptibility to PMPA. Van Rompay, Koen K. A.; Cherrington, Julie M.; Marthas, Marta L.; Lamy, Patrick D.; Dailey, Peter J.; Canfield, Don R.; Tarara, Ross P.; Bischofberger, Norbert; Pedersen, Niels C. (California Regional Primate Research Center, University of California, Davis, CA, 95616, USA). Antimicrob. Agents Chemother., 43(4), 802-812 (English) 1999. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.

AB Simian immunodeficiency virus (SIV) infection of newborn rhesus macaques is a useful animal model of human immunodeficiency virus infection for the study of the emergence and clin. implications of drug-resistant viral mutants. We previously demonstrated that SIV-infected infant macaques receiving prolonged treatment with 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) developed viral mutants with fivefold reduced susceptibility to PMPA in vitro and that the development of these mutants was assocd. with the development of a K65R mutation and addnl. compensatory mutations in reverse transcriptase (RT). To study directly the virulence and clin. implications of these SIV mutants, two uncloned SIVmac isolates with similar fivefold reduced in vitro susceptibilities to PMPA but distinct RT genotypes, SIVmac055 (K65R, N69T, R82K A158S, S211N) and SIVmac385 (K65R, N69S, I118V), were each inoculated i.v. into six newborn rhesus macaques; 3 wk later, three animals of each group were started on PMPA treatment. All six untreated animals developed persistently high levels of viremia and fatal immunodeficiency within 4 mo. In contrast, the six PMPA-treated animals, despite having persistently high virus levels, survived significantly longer: 5 to 9 mo for the three SIVmac055-infected infants and .gtoreq.21 mo for the three SIVmac385-infected infants. Virus from only one untreated animal demonstrated reversion to wild-type susceptibility and loss of the K65R mutation. In several other animals, addnl. RT mutations, including K64R and Y115F, were detected, but the biol. role of these mutations is unclear since they did not affect the in vitro susceptibility of the virus to PMPA. In conclusion, this study demonstrates that although SIVmac mutants with the PMPA-selected K65R mutation in RT were highly virulent, PMPA treatment still offered strong therapeutic benefits. These results suggest that the potential emergence of HIV mutants with reduced susceptibility to PMPA in patients during prolonged PMPA therapy may not eliminate its therapeutic benefits.

REFERENCE 3: 131:13412 Early short-term 9-[2-(R)-(phosphonomethoxy)propyl]adenine treatment favorably alters the subsequent disease course in simian immunodeficiency virus-infected newborn rhesus macaques. Van Rompay, Koen K. A.; Dailey, Peter J.; Tarara, Ross P.; Canfield, Don R.; Aguirre, Nancy L.; Cherrington, Julie M.; Lamy, Patrick D.; Bischofberger, Norbert; Pedersen, Niels C.; Marthas, Marta L. (California Regional Primate Research Center, University of California, Davis, CA, 95616, USA). J. Virol., 73(4), 2947-2955 (English) 1999. CODEN: JOVIAM. ISSN: 0022-538X. Publisher: American Society for Microbiology.

AB Simian immunodeficiency virus (SIV) infection of newborn macaques is a useful animal model of human pediatric AIDS to study disease pathogenesis and to develop intervention strategies aimed at delaying disease. In the present study, we demonstrate that very early events of infection greatly det. the ultimate disease course, as short-term antiviral drug administration during the initial viremia stage significantly delayed the onset of AIDS. Fourteen newborn macaques were inoculated orally with uncloned, highly virulent SIVmac251. The four untreated control animals

showed persistently high virus levels and poor antiviral immune responses;
they developed fatal immunodeficiency within 15 wk. In contrast, SIV-infected newborn macaques which were started on 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) treatment at 5 days of age and continued for either 14 or 60 days showed reduced virus levels and enhanced antiviral immune responses. This short-term PMPA treatment did not induce detectable emergence of SIV mutants with reduced in vitro susceptibility to PMPA. Although viremia increased in most animals after PMPA treatment was withdrawn, all animals remained disease-free for at least 6 mo. Our data suggest that short-term treatment with a potent antiviral drug regimen during the initial viremia will significantly prolong AIDS-free survival for HIV-infected infants and adults.

REFERENCE 4: 130:296895 (R)-PMPA and Bis(POC)PMPA: Anti-HIV. Sorbera, L. A.; Castaner, J. (Prous Science, Barcelona, 08080, Spain). Drugs Future, 23(12), 1279-1286 (English) 1998. CODEN: DRFUD4. ISSN: 0377-8282. Publisher: Prous Science.
AB Review with 40 refs. on the synthesis and pharmaciol. of the title compds.

REFERENCE 5: 130:177176 Comparison of antiviral compounds against human herpesvirus 6 and 7. Yoshida, Mariko; Yamada, Masao; Tsukazaki, Takashi; Chatterjee, Subhendra; Lakeman, Fred D.; Nii, Shiro; Whitley, Richard J. (Department of Virology, Okayama University Medical School, Okayama, 700-8558, Japan). Antiviral Res., 40(1-2), 73-84 (English) 1998. CODEN: ARSRDR. ISSN: 0166-3542. Publisher: Elsevier Science B.V..
AB Four classes of antiviral compds. were evaluated for inhibitory activity against two variants of human herpesvirus 6 (HHV-6A and -6B) and human herpesvirus 7 (HHV-7). These included: (1) a pyrophosphate analog, phosphonoformic acid (PFA); (2) beta-guanine analogs, 9-(2-hydroxyethoxymethyl)guanine (acyclovir or ACV), 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine (ganciclovir or GCV) and 9-(4-hydroxy-3-hydroxy-3-hydroxymethylbutylyl)guanine (penciclovir or PCV); (3) acyclic nucleoside phosphonates, (S)-1-[(3-hydroxy-2-phosphonylmethoxy)propyl]cytosine [cidofovir or (S)-HPMPC] and its cyclic deriv. (S)-cyclic-HPMPC (cHPMPC), 9-[[(2-hydroxy-1-phosphonomethoxy)ethoxy]methyl]guanine (HPMEMG) and 9-[(2-phosphonylmethoxy)ethyl]-2,6-diaminopurine (PMEDAP), and the seven other related compds.; and (4) a series of benzimidazole ribonucleosides, including 2-bromo-5,6-dichloro-1-(beta-D-ribofuranosyl)benzimidazole (BDCRB). End-point inhibitory concn. (EPC) and 50% effective inhibitory concn. (EC50) values were detd. by a dot-blot antigen detection method in cord blood mononuclear cells infected with HHV-6A, HHV-6B or HHV-7 at a multiplicity of infection of 0.004 CCID50/cell. (S)-HPMPC and cHPMPC had an EC50 value of approx. 0.3 .mu.g/mL for HHV-6A, 1.2 .mu.g/mL for HHV-6B and 3.0 .mu.g/mL for HHV-7. These compds. were the most active of those tested against each virus. The EC50 value of GCV for HHV-6A was 0.65 .mu.g/mL, 1.33 .mu.g/mL for HHV-6B, and >7 .mu.g/mL for HHV-7. The EC50 values of ACV and PCV were approx. 6-8 .mu.g/mL for HHV-6A, 16-24 .mu.g/mL
for HHV-6B and 121-128 .mu.g/mL for HHV-7. These drugs were the least active. The sensitivity of HHV-7 to the guanine analogs was different from HHV-6, suggesting a difference in selectivity of specific viral enzymes.

REFERENCE 6: 130:158419 Antiviral nucleotide analog composition and synthesis method. Munger, John D., Jr.; Rohloff, John C.; Schultze, Lisa M. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9905150 A1 19990204, 43 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA,
CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS,

JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US15254 19980723. PRIORITY: US 1997-900752 19970725; US 1997-53777 19970725.

AB The invention provides a compn. comprising 9-[2-(R)-[[Bis[[(isopropoxycarbonyl)oxy]methoxy]phosphinoyl]methoxy]propyl]adenine [bis(POC)PMPA] and fumaric acid (1:1) for oral delivery of (R)-9-[2-(phosphonomethoxy)propyl]adenine (PMPA). The compn. is useful as an intermediate for the prepn. of antiviral compds., or is useful for administration to patients for antiviral therapy or prophylaxis. The compn. is particularly useful when administered orally. The invention also provides methods to make PMPA and intermediates in PMPA synthesis. Embodiments include lithium t-butoxide, 9-(2-hydroxypropyl)adenine and di-Et p-toluenesulfonylmethoxy-phosphonate in an org. solvent such as DMF. The reaction results in di-Et PMPA prepns. contg. an improved byproduct profile compared to di-Et PMPA made by prior methods. "Bis(POC)PMPA" fumarate, or BPPF, was prepd. in 7 steps via reaction of (R)-4-methyl-1,3-dioxolan-2-one with adenine and etherification of the product with (EtO)2P(O)CH2-OTs.

REFERENCE 7: 130:60635 Selective inhibition of HIV-1 reverse transcriptase by an antiviral inhibitor, (R)-9-(2-phosphonylmethoxypropyl)adenine. Suo, Zucai; Johnson, Kenneth A. (Department of Biochemistry and Molecular Biology, the Pennsylvania State University, University Park, PA, 16802, USA). J. Biol. Chem., 273(42), 27250-27258 (English) 1998. CODEN: JBCHA3. ISSN: 0021-9258. Publisher: American Society for Biochemistry and Molecular Biology.

AB (R)-9-(2-Phosphonylmethoxypropyl)adenine (PMPA) is an acyclic nucleoside phosphonate that has been shown to be effective in the treatment of AIDS although it has a shorter sepn. between the adenine and phosphorus than dideoxy-AMP and dAMP. By using presteady state kinetic methods, we examd. the incorporation of the diphosphate of PMPA, 2',3'-dideoxyadenosine 5'-triphosphate (ddATP), and dATP catalyzed by wild-type human immunodeficiency virus type 1 (HIV-1) reverse transcriptase, an exonuclease-deficient T7 DNA polymerase (T7 exo-), and wild-type rat DNA polymerase .beta. to evaluate the selectivity of PMPA as an antiviral inhibitor. With a DNA/DNA or DNA/RNA 22/43-mer duplex, the diphosphate of PMPA (PMPApp) is as effective as ddATP in reactions catalyzed by HIV-1 reverse transcriptase in that both analogs have similar substrate specificity consts. (kp/Kd) which are only 5-fold lower than dATP. In contrast, PMPApp is a much weaker inhibitor of the reaction catalyzed by T7 exo- (with the DNA/DNA 22/43-mer duplex) in that PMPApp has a 5.times.10-4-fold lower kp/Kd than ddATP and dATP. The lower kp/Kd of PMPApp is due to a 1000-2000-fold lower incorporation rate (kp) and a 35-45-fold lower binding const. (Kd). Similarly, PMPApp is 800-fold less inhibitory toward polymerase .beta. with the DNA/DNA 22/43-mer duplex, whereas in studies with a single nucleotide gapped DNA (22-20/43-mer) PMPApp is 13-fold less inhibitory than ddATP. Although parallel studies will need to be performed using appropriate human polymerases, these results begin to define the mechanistic basis for the reported lower toxicity of PMPA in the treatment of AIDS.

REFERENCE 8: 130:253 Potent differentiation-inducing properties of the

antiretroviral agent 9-(2-phosphonylmethoxyethyl)adenine (PMEA) in the rat
choriocarcinoma (RCHO) tumor cell model. Hatse, Sigrid; Naesens, Lieve; De Clercq, Erik; Balzarini, Jan (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.). Biochem. Pharmacol., 56(7), 851-859 (English) 1998. CODEN: BCPCA6. ISSN: 0006-2952. Publisher: Elsevier Science Inc..

AB 9-(2-Phosphonylmethoxyethyl)adenine (PMEA) and its closely related structural analog (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA) are potent inhibitors of retroviruses and hepatitis B virus. In its oral prodrug from (adefovir dipivoxil), PMEA is currently the subject of advanced phase II/III clin. trials for the treatment of HIV infections. PMEA has also been shown to be a potent differentiation-inducing agent. In the present study, PMEA was found to have a strong differentiation-inducing effect on rat choriocarcinoma (RCHO) cells, comparable to that of methotrexate, which is the drug of choice for the chemotherapy of choriocarcinoma in humans. PMEA induced differentiation of choriocarcinoma trophoblast cells in a concn.-dependent manner within the 2- to 50-.mu.M concn. range, as ascertained by giant cell formation, alk. phosphatase induction, progesterone secretion, and the disappearance of a cytotrophoblast-sp. surface antigen. PMEA had to be exposed to the rat choriocarcinoma cell cultures for at least 2-3 days to achieve optimal growth inhibition and differentiation of the tumor cells. Unlike PMEA, PMPA failed to induce differentiation of proliferating cytotrophoblasts into nonproliferating, hormonally active giant cells. This points to the specificity of PMEA as an inducer of choriocarcinoma cell differentiation.

REFERENCE 9: 129:310454 Safety, pharmacokinetics, and antiretroviral activity of intravenous 9-[2-(R)-(phosphonomethoxy)propyl]adenine, a novel anti-human immunodeficiency virus (HIV) therapy, in HIV-infected adults. Deeks, Steven G.; Barditch-Crovo, Patricia; Lietman, Paul S.; Hwang, Frances; Cundy, Kenneth C.; Rooney, James F.; Hellmann, Nicholas S.; Safrin, Sharon; Kahn, James O. (University of California, San Francisco, San Francisco, CA, USA). Antimicrob. Agents Chemother., 42(9), 2380-2384 (English) 1998. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.

AB 9-[2-(R)-(Phosphonomethoxy)propyl]adenine (PMPA) is a nucleotide analog with potent antiretroviral activity in vitro and in simian models. A randomized, double-blind, placebo-controlled, dose-escalation clin. trial of i.v. PMPA monotherapy was conducted in HIV-infected adults with CD4 cell counts of .gtoreq.200 cells/mm3 and plasma HIV RNA levels of .gtoreq.10,000 copies/mL. Two dose levels were evaluated (1 and 3 mg/kg/day). On day 1, a single dose of PMPA or placebo was administered by i.v. infusion. Beginning on day 8, PMPA or placebo was administered once daily for an addnl. 7 consecutive days. All the subjects tolerated the treatment without significant adverse events. Mean peak serum PMPA concns. were 2.7 and 9.1 .mu.g/mL in the 1- and 3-mg/kg cohorts, resp. Serum concns. declined in a biexponential fashion, with a terminal half-life of 4-8 h. At 3 mg/kg/day, a single infusion of PMPA resulted in a 0.4 log10 median decline in plasma HIV RNA by day 8. Following 7 consecutive days of drug administration thereafter, the median changes in plasma HIV RNA from basal values were -1.1, -0.6, and 0.1 log10 in the 3-mg/kg/day, 1-mg/kg/day, and placebo dose groups, resp. Following the final dose in the 3-mg/kg/day cohort, the redn. in HIV RNA was sustained for 7 days before returning toward initial values.

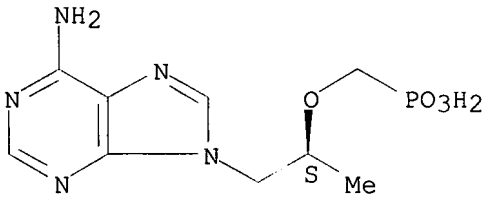
REFERENCE 10: 129:211274 Two doses of PMPA protect newborn macaques against

oral simian immunodeficiency virus infection. Van Rompay, Koen K. A.; Berardi, Christopher J.; Aguirre, Nancy L.; Bischofberger, Norbert; Lietman, Paul S.; Pedersen, Niels C.; Marthas, Marta L. (California Regional Primate Research Center, University of California, Davis, CA, 95616, USA). AIDS (London), 12(9), F79-F83 (English) 1998. CODEN: AIDSET. ISSN: 0269-9370. Publisher: Lippincott-Raven Publishers.

AB Simple and affordable intervention strategies are needed to reduce the rate of HIV transmission from mother to infant in developing countries. Simian immunodeficiency virus (SIV) infection of newborn rhesus macaques is considered to be a useful model of human pediatric HIV infection. To investigate whether short-term 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) administration can protect newborn rhesus macaques against perinatal SIV infection. Eight newborn macaques were inoculated orally with highly virulent SIVmac within the first 3 days of life. Four of these animals were untreated controls. The other four animals were given one dose of PMPA (30 mg/kg s.c.) 4 h before oral SIV inoculation, and were then given a second and final dose of PMPA 24 h later. All four untreated control animals were persistently SIV-pos. within 2 wk after virus inoculation. In contrast, no virus could be detected in the four animals that received two doses of PMPA; these animals were seroneg. and healthy at 10 mo. Two doses of PMPA prevented SIV infection of newborn macaques. Our data suggest that short-term administration of PMPA to HIV-infected pregnant women at the onset of labor and to their newborns after delivery may reduce the rate of intrapartum HIV transmission.

L5 ANSWER 40 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 147127-19-3 REGISTRY
CN Phosphonic acid, [[(1S)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, (S)-
OTHER NAMES:
CN (S)-9-(2-Phosphonomethoxypropyl)adenine
FS STEREOSEARCH
MF C9 H14 N5 O4 P
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, DRUGNL, DRUGUPDATES, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



14 REFERENCES IN FILE CA (1967 TO DATE)
14 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:163201 Treatment of conditions of abnormally increased intraocular pressure by administration of phosphonylmethoxyalkyl nucleoside analogs and related nucleoside analogs. Freeman, William R. (USA). U.S. US 5869468 A 19990209, 13 pp., Cont.-in-part of U.S. Ser.

No. 360,995. (English). CODEN: USXXAM. APPLICATION: US 1995-440447 19950512. PRIORITY: US 1994-222128 19940404; US 1994-360995 19941220.

AB Methods are provided for treatment of conditions of abnormally increased intraocular pressure, particularly those caused by glaucoma, by administration of phosphonylmethoxyalkyl nucleoside analogs. Compns. formulated and packaged for intraocular administration for use in the methods are also provided. Administration of the compd. may be by intravitreal injection, aq. humor injection, injection into the external layers of the eye, e.g. subconjunctival injection or subtenon injection, or may be, when penetrating derivs. are used, by topical application to the eye. The degree of redn. in pressure is dosage-dependent, and significant redn. in pressure is obtained. A single injection can produce prolonged, and perhaps permanent, lowering of the intraocular pressure.

REFERENCE 2: 129:90065 Immunomodulatory properties of antiviral acyclic nucleotide analogs: cytokine stimulatory and nitric oxide costimulatory effects. Zidek, Zdenek; Holy, Antonin; Frankova, Daniela (Institute of Pharmacology, Academy of Sciences of the Czech Republic, Prague, 142 20/4, Czech Rep.). Int. J. Immunopharmacol., Volume Date 1997, 19(9/10), 587-597 (English) 1998. CODEN: IJIMDS. ISSN: 0192-0561. Publisher: Elsevier Science Ltd..

AB Acyclic nucleotide analogs exhibit strong activity against a broad range of viruses, including HIV-1 and -2. Their effects on in vitro secretion of cytokines and prodn. of nitric oxide (NO) by murine peritoneal macrophages, factors known to play a role in virus replication, were investigated. Included in the study were the most prominent compds. of the series: 9-(2-phosphonomethoxyethyl)adenine, 9-(2-phosphonomethoxyethyl)-2,6-diaminopurine, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine [(R)- or (S)-PMPA], (R)- and (S)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine [(R)- or (S)-PMPDAP], 9-(2-phosphonomethoxyethyl)guanine (PMEG), and (S)-1-(3-hydroxy-2-phosphonomethoxypropyl)cytosine [(S)-HPMPC]. PMEG, (R)-PMPA, and (S)-PMPA greatly enhanced the secretion of both tumor necrosis factor-.alpha. (TNF-.alpha.) and interleukin-10 (IL-10), (R)-PMPDAP stimulated only TNF-.alpha., other test compds. were ineffective. None of them influenced the secretion of IL-2 or interferon-.gamma. (IFN-.gamma.). Both TNF-.alpha. and IL-10 have been found to be major factors detg. enhancing effects of PMEG, (R)-PMPA, and (S)-PMPA on prodn. of NO generated by exogenous IFN-.gamma.. The study points to a possible implication of immunomodulatory properties in the antiviral effects of some acyclic nucleotide analogs. In addn., the data support the view that endogenous IL-10 can stimulate certain macrophage functions.

REFERENCE 3: 127:44486 Acyclic phosphonomethylether nucleoside inhibitors of respiratory viruses. Barnard, D. L.; Bischofberger, N.; Kim, C. U.; Huffman, J. H.; Sidwell, R. W.; Dougherty, J. p.; Lew, W.; Williams, M. A.; Yang, W. (Inst. Antiviral Res., Utah State Univ., Logan, UT, 84322-5600, USA). Antiviral Chem. Chemother., 8(3), 223-233 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB A series of acyclic phosphonomethylether nucleosides were synthesized and then evaluated for inhibitory activity against respiratory viruses of clin. significance using CPE inhibition, neutral red uptake and virus yield redn. assays. Of the 20 compds. synthesized, none significantly inhibited influenza A or B viruses or respiratory syncytial virus strains A2, Long or 18537; the selective indexes (SI) were less than 10. A new

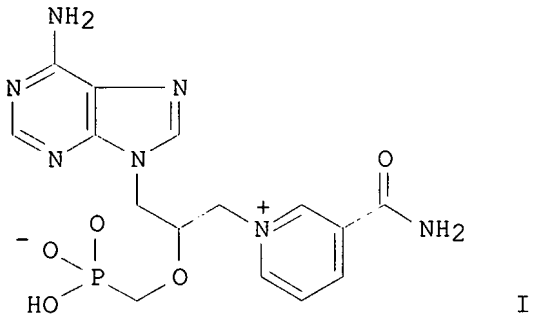
compd., GS-2128 (2R, 5R-9-[2,5-dihydro-5-(phosphonomethoxy)-2-furanyl]adenine; D4APl), selectively inhibited adenovirus 5 (Sl>10) as did GS-0577 (9-(3-hydroxy-2-phosphonylmethoxypropyl)-adenine; HPMPA) and GS-0504 [(S)-1-[3-hydroxy-2-(phosphonylmethoxypropyl)]-cytosine; HPMPC]. The 50% effective concns. (EC50) ranged from 8-100 .mu.g mL-1 and 50% cell inhibitory concns. (CC50) from 40-1000 .mu.g mL-1. All three compds. were also found to be active against lab. strains and clin. isolates of adenovirus type 1, 2, 8 and 41 with EC50 values ranging from 0.2 to 10 .mu.g mL-1. Two compds., GS-438 (9-(2-phosphonylmethoxy-ethyl)guanine, PMEG) and GS-2542 (9-[(3-phosphonomethoxy)methoxymethyl]guanine) inhibited parainfluenza virus 3 strain C243, with Sl of 52 >333, resp. PMEG also inhibited measles virus strains CC, Halonen and Chicago with EC50 values ranging from 0.03-9 .mu.g mL-1. These data suggest that these compds. should be considered for possible development as therapeutic agents for respiratory virus infections.

REFERENCE 4: 126:144493 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Masojidkova, Milena; Holy, Antonin (Inst. Organic Chem. Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(10), 1538-1548 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765. Publisher: Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic.

AB "Abbreviated" NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties, 9-(2-phosphonomethoxyethyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine 2-(3-carbamoylpyridinium)ethyl ester, (RS)-9-(3-hydroxy-2-phosphonomethoxypropyl)adenine 2-(3-carbamoyl-pyridinium)ethyl ester, and (S)- and (R)-1-[3-(adenin-9-yl)-2-phosphonatomethoxypropyl]-3-carbamoylpyridinium, were prepd. by multistep syntheses using the Zincke reaction in the last step. The cytostatic activity of title NAD+ analogs was tested on L-1210 mouse leukemia cells. None of the compds. exhibited significant cytostatic activity and neither were cytotoxic. In vitro activities against DNA viruses and retroviruses were detd. (no data).

REFERENCE 5: 125:301463 "Abbreviated" NAD+ analogs containing a phosphonate function. Hockova, Dana; Holy, Antonin (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S52-S54 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

GI



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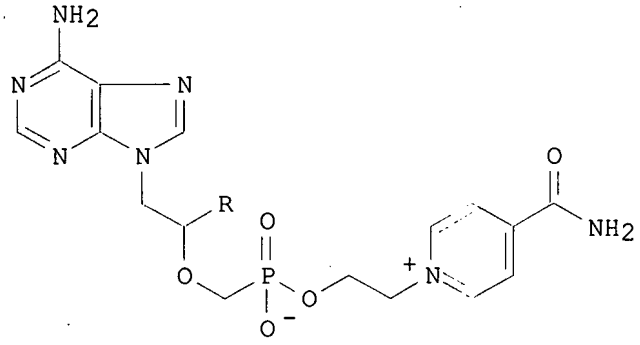


II

AB New types of NAD+ analogs with anionic phosphonate function as a part of the link between the adenine and nicotinamide moieties were prepd. by multistep syntheses using the Zincke reaction as the last step. The structures of the compds. were derived from the biol. active acyclic nucleotide analogs. Example compds. were (R)-I and (S)-I. None of the compds. thus prepd. showed significant co-enzymic activity. However, (R)-I and (S)-I possessed antiviral activity. Also prepd. were the NAD+ analogs II (R = H, Me, etc.).

REFERENCE 6: 125:292255 Inhibition of murine lymphocyte proliferation by N6-substituted acyclic purine nucleoside phosphonates. Holy, Antonin; Zidek, Zdenek; Votruba, Ivan (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S182-S187 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

AB Acyclic nucleoside phosphonate analogs substituted at the N6-position of the adenine and 2,6-diaminopurine ring exhibit remarkable inhibitory effects on mitogen-stimulated proliferation of murine spleen lymphocytes at concns. (IC50) starting from 10 nM. The effect depends on both phosphonomethoxyalkyl side chain and N6-substituents. Mitogen-stimulated T-cells were affected at much lower concns. than mitogen-stimulated B-cells.

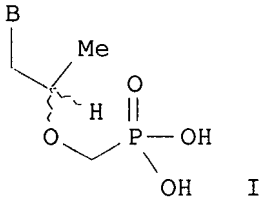
REFERENCE 7: 124:249758 Activity of the (R)-enantiomers of 9-(2-phosphonylmethoxypropyl)-adenine and 9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine against human immunodeficiency virus in different human cell systems. Balzarini, J.; Aquaro, S.; Perno, C.-F.; Witvrouw, M.; Holy, A.; De Clercq, E. (Rega Institute Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.). Biochem. Biophys. Res. Commun., 219(2), 337-41 (English) 1996. CODEN: BBRCA9. ISSN: 0006-291X.

AB The (S)- and (R)-enantiomers of 9-(2-phosphonylmethoxypropyl) derivs. of adenine (PMPA) and 2,6-diaminopurine (PMPDAP) were evaluated for their inhibitory effect on HIV replication in several human cell systems,

including natural peripheral blood lymphocytes (PBL) and freshly isolated monocyte/macrophages (M/M). The (R)-enantiomers of PMPDAP and PMPA were .apprx.10- to 100-fold more effective against HIV than their (S)-enantiomeric counterparts. The antiviral efficacy of (R)-PMPA was comparable to that of the prototype acyclic nucleoside phosphonate 9-(2-phosphonylmethoxyethyl)adenine (PMEA). The most potent and selective HIV inhibitor was (R)-PMPDAP. Its 50% effective concn. ranged from 0.01 .mu.M for HIV-1/Ba-L in M/M to 1-2.8 .mu.M for HIV-1/IIIB and HIV-1/HE in C8166, CEM, Molt/4, MT-4 and PBL cells. Both (R)-PMPA and (R)-PMPDAP were not toxic to the host cells at 300 .mu.M.

REFERENCE 8: 124:146698 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. II. The synthon approach. Holy, Antonin; Dvorakova, Hana; Masojidkova, Milena (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(8), 1390-409 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.

GI

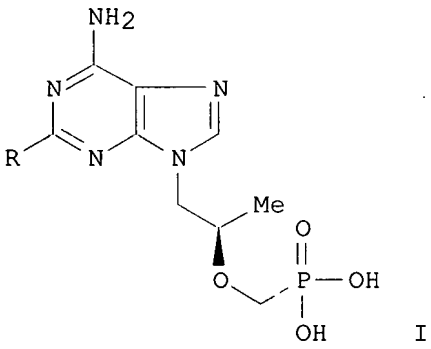


I

AB Acyclic nucleotides, e.g. I (B = adenine, guanine, hypoxanthine), were prepd. from the corresponding 1-benzyloxy-2-propanol.

REFERENCE 9: 124:117829 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. I. The stepwise approach. Holy, Antonin; Masojidkova, Milena (Inst. Org. Chem. Biochem., Acad. Sci., Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(7), 1196-212 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.

GI



I

AB Phosphonomethoxypropyl acyclic nucleotide analogs, e.g. I (R = H, NH2), were prepd. via alkylation of N-protected N-(2-hydroxypropyl) derivs. of the corresponding bases with bis(2-propyl) p-toluenesulfonyloxymethylphosphonate. This approach was used for the synthesis of cytosine, adenine and 2,6-diaminopurine derivs., while compds. derived from guanine were prepd. by hydrolysis of 2-amino-6-chloropurine intermediates.

REFERENCE 10: 124:110665 Kinetic properties of adenine nucleotide analogs against purified 5-phosphoribosyl-1-pyrophosphate synthetase from E. coli, rat liver and human erythrocytes. Balzarini, J.; Nave, J.-F.; Becker, M. A.; Tatibana, M.; De Clercq, E. (Rega Inst. for Medical Research, Katholieke Univ. Leuven, Louvain, B-3000, Belg.). Nucleosides Nucleotides, 14(9 & 10), 1861-71 (English) 1995. CODEN: NUNUD5. ISSN: 0732-8311.

AB The nucleoside analog 2',3'-dideoxyadenosine (ddA), the phosphonate isostere of 2',3'-dideoxy-2',3'-didehydro-adenosine (d4A) 5'-monophosphate (d4API), and the acyclic nucleoside phosphonates PMEoA, PMEA, FPMPA and PMPA are potent and selective antiretroviral agents. The authors found that these compds. are recognized as substrates by the PRPP synthetases from E. coli, rat liver and human erythrocytes, as their monophosphate and triphosphate form in the reverse and forward reaction, resp. In particular, ddA-5'-monophosphate (ddAMP) and ddA-5'-triphosphate proved to be excellent substrates for the enzymes. D4API was a relatively good substrate of the rat liver and human erythrocyte PRPP synthetases. The acyclic nucleoside phosphonates were rather poor substrates, as evident from their low Vmax values. None of the PRPP synthetases are found to act stereospecifically: they recognized both the S- and R-enantiomers of FPMPA and PMPA in a comparably efficient manner. The data indicate that PRPP synthetase may recognize a much broader range of adenine nucleotide analogs than previously thought.

L5 ANSWER 41 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 147057-10-1 REGISTRY
CN Phosphonic acid, [[(1R)-2-(2,6-diamino-9H-purin-9-yl)-1-methylethoxy]methyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[2-(2,6-diamino-9H-purin-9-yl)-1-methylethoxy]methyl]-, (R)-
OTHER NAMES:
CN (R)-9-(2-Phosphonomethoxypropyl)-2,6-diaminopurine
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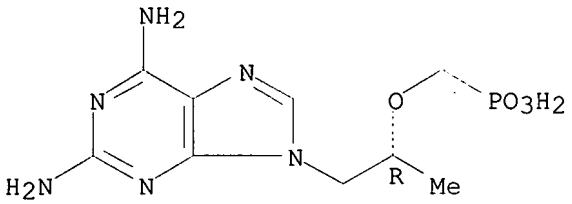
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXLIT

Absolute stereochemistry.



18 REFERENCES IN FILE CA (1967 TO DATE)
18 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:130905 Inhibitory effects of novel nucleoside and nucleotide analogs on Epstein-Barr virus replication. Meerbach, A.; Holy, A.; Wutzler, P.; De Clercq, E.; Neyts, J. (Institute for Antiviral Chemotherapy, Friedrich-Schiller-University Jena, Erfurt, D-99089, Germany). Antiviral Chem. Chemother., 9(3), 275-282 (English) 1998. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB The anti-Epstein-Barr virus (EBV) activity of different classes of compds. was assessed by means of an EBV DNA hybridization assay using a digoxigenin-labeled probe specific for the BamHI W fragment of the EBV genome, as well as by measuring viral capsid antigen (VCA) expression after a 7 day incubation period of P3HR-1 producer cells with the test substances. Several compds. proved to be potent and selective inhibitors of EBV DNA synthesis and VCA expression. Of the new compds. that were evaluated for their anti-EBV activity, the highest efficacy (lowest EC50) and highest selectivity index (SI) were shown by 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]purine (S 2242) (EC50 0.6 ng/mL; SI 600), 9-[2-(phosphonomethoxy)ethyl]-6-(dimethylamino)purine (EC50 1.1 .mu.g/mL; SI 91), 9-[2-(phosphonomethoxy)ethyl]-2-amino-6-(benzhydrylamino)purine (EC50 1.3 .mu.g/mL; SI 29), 7-[2-(phosphonomethoxy)ethyl]-6-(dimethylamino)purine (EC50 0.8 .mu.g/mL; SI 56), 9-[(R)-2-(phosphonomethoxy)propyl]-6-[[2-(dimethylamino)ethyl]amino]purine (ECs50 0.5 .mu.g/mL; SI 42), 3'-oximino-2',3'-dideoxythymidine (EC50 1.5 g/mL; SI 65), and 1-[2,3-dideoxy-3-(hydroxyamino)-.beta.-D-threo-pentofuranosyl]thymine (EC50 4.1 .mu.g/mL; SI >24).

REFERENCE 2: 129:90065 Immunomodulatory properties of antiviral acyclic nucleotide analogs: cytokine stimulatory and nitric oxide costimulatory effects. Zidek, Zdenek; Holy, Antonin; Frankova, Daniela (Institute of Pharmacology, Academy of Sciences of the Czech Republic, Prague, 142 20/4, Czech Rep.). Int. J. Immunopharmacol., Volume Date 1997, 19(9/10), 587-597 (English) 1998. CODEN: IJIMDS. ISSN: 0192-0561. Publisher: Elsevier Science Ltd..

AB Acyclic nucleotide analogs exhibit strong activity against a broad range of viruses, including HIV-1 and -2. Their effects on in vitro secretion of cytokines and prodn. of nitric oxide (NO) by murine peritoneal macrophages, factors known to play a role in virus replication, were investigated. Included in the study were the most prominent compds. of the series: 9-(2-phosphonomethoxyethyl)adenine, 9-(2-phosphonomethoxyethyl)-2,6-diaminopurine, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine [(R)- or (S)-PMPA], (R)- and (S)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine [(R)- or (S)-PMPDAP], 9-(2-phosphonomethoxyethyl)guanine (PMEG), and (S)-1-(3-hydroxy-2-phosphonomethoxypropyl)cytosine [(S)-HPMPC]. PMEG, (R)-PMPA, and (S)-PMPA

greatly enhanced the secretion of both tumor necrosis factor-.alpha. (TNF-.alpha.) and interleukin-10 (IL-10), (R)-PMPDAP stimulated only TNF-.alpha., other test compds. were ineffective. None of them influenced the secretion of IL-2 or interferon-.gamma. (IFN-.gamma.). Both TNF-.alpha. and IL-10 have been found to be major factors detg. enhancing effects of PMEG, (R)-PMPA, and (S)-PMPA on prodn. of NO generated by exogenous IFN-.gamma.. The study points to a possible implication of immunomodulatory properties in the antiviral effects of some acyclic nucleotide analogs. In addn., the data support the view that endogenous IL-10 can stimulate certain macrophage functions.

REFERENCE 3: 128:97307 Genotoxicity of purine acyclic nucleotide analogs. Otova, B.; Holy, A.; Votruba, I.; Sladka, M.; Bila, V.; Mejsnarova, B.; Leskova, V. (Department of Biology, 1st Faculty of Medicine, Charles University, Prague, 128 00/2, Czech Rep.). Folia Biol. (Prague), 43(6), 225-229 (English) 1997. CODEN: FOBLAN. ISSN: 0015-5500. Publisher: Institute of Molecular Genetics.

AB The genotoxic and embryotoxic effects of phosphonomethoxyalkylpurines, a new group of antiviral agents, decrease in the following order: PMEG>PMEthioG>PMEDAP>PMEA>(R)-PMPDAP=(R)-PMPA. Results of the present study are fully consistent with the previously found efficacy of their diphosphates to inhibit the replicative DNA polymerases. The marked genotoxicity of PMEG and PMEthioG is comparable to that of mitomycin C, whereas the moderate genotoxicity of PMEA is comparable to that of AZT. (R)-PMPDAP and (R)-PMPA did not induce any structural aberrations of chromosomes under the exptl. conditions.

REFERENCE 4: 127:44486 Acyclic phosphonomethylether nucleoside inhibitors of respiratory viruses. Barnard, D. L.; Bischofberger, N.; Kim, C. U.; Huffman, J. H.; Sidwell, R. W.; Dougherty, J. p.; Lew, W.; Williams, M. A.; Yang, W. (Inst. Antiviral Res., Utah State Univ., Logan, UT, 84322-5600, USA). Antiviral Chem. Chemother., 8(3), 223-233 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB A series of acyclic phosphonomethylether nucleosides were synthesized and then evaluated for inhibitory activity against respiratory viruses of clin. significance using CPE inhibition, neutral red uptake and virus yield redn. assays. Of the 20 compds. synthesized, none significantly inhibited influenza A or B viruses or respiratory syncytial virus strains A2, Long or 18537; the selective indexes (SI) were less than 10. A new compd., GS-2128 (2R, 5R-9-[2,5-dihydro-5-(phosphonomethoxy)-2-furanyl]adenine; D4APl), selectively inhibited adenovirus 5 (Sl>10) as did GS-0577 (9-(3-hydroxy-2-phosphonylmethoxypropyl)-adenine; HPMPA) and GS-0504 [(S)-1-[3-hydroxy-2-(phosphonylmethoxypropyl)]-cytosine; HPMPC]. The 50% effective concns. (EC50) ranged from 8-100 .mu.g mL-1 and 50% cell inhibitory concns. (CC50) from 40-1000 .mu.g mL-1. All three compds. were also found to be active against lab. strains and clin. isolates of adenovirus type 1, 2, 8 and 41 with EC50 values ranging from 0.2 to 10 .mu.g mL-1. Two compds., GS-438 (9-(2-phosphonylmethoxy-ethyl)guanine, PMEG) and GS-2542 (9-[(3-phosphonomethoxy)methoxymethyl]guanine) inhibited parainfluenza virus 3 strain C243, with Sl of 52 >333, resp. PMEG also inhibited measles virus strains CC, Halonen and Chicago with EC50 values ranging from 0.03-9 .mu.g mL-1. These data suggest that these compds. should be considered for possible development as therapeutic agents for respiratory virus infections.

REFERENCE 5: 126:31584 acyclic nucleosides as virucides and immunostimulation suppressants. Holy, Antonin; De Clercq, Erik Desire Alice (Ustav Organicke Chemie A Biochemie Akademie Ved C, Czech Rep.; De Clercq, Erik Desire Alice; Holy, Antonin; De Clercq, Erik, Desire, Alice).
PCT Int. Appl. WO 9633200 A1 19961024, 57 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-CZ11 19960419. PRIORITY: US 1995-426372 19950421.

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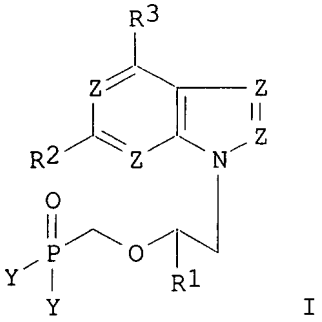

I

AB Acyclic nucleosides I [R1 = Me, C.tplbond.CH, CH:CH2, CH2F, azidomethyl; R2,R3 = H, NH2, alkylamine, alkoxyalkylamine; Y = OH, alkoxy, alkaryloxy, aryloxy, OPO3H2, OP2O6H2, aminoacid amidate, polypeptide amidate; Z = N, CH] were prepd. Thus, 6-amino-9-(R)-(2-phosphonomethoxypropyl)adenine was tested as virucides and immunostimulation suppressants.

REFERENCE 6: 125:292255 Inhibition of murine lymphocyte proliferation by N6-substituted acyclic purine nucleoside phosphonates. Holy, Antonin; Zidek, Zdenek; Votruba, Ivan (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S182-S187 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

AB Acyclic nucleoside phosphonate analogs substituted at the N6-position of the adenine and 2,6-diaminopurine ring exhibit remarkable inhibitory effects on mitogen-stimulated proliferation of murine spleen lymphocytes at concns. (IC50) starting from 10 nM. The effect depends on both phosphonomethoxyalkyl side chain and N6-substituents. Mitogen-stimulated T-cells were affected at much lower concns. than mitogen-stimulated B-cells.

REFERENCE 7: 124:249758 Activity of the (R)-enantiomers of 9-(2-phosphonylmethoxypropyl)-adenine and 9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine against human immunodeficiency virus in different human cell systems. Balzarini, J.; Aquaro, S.; Perno, C.-F.; Witvrouw, M.; Holy, A.; De Clercq, E. (Rega Institute Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.). Biochem. Biophys. Res. Commun., 219(2), 337-41 (English) 1996. CODEN: BBRCA9. ISSN: 0006-291X.

AB The (S)- and (R)-enantiomers of 9-(2-phosphonylmethoxypropyl) derivs. of adenine (PMPA) and 2,6-diaminopurine (PMPDAP) were evaluated for their inhibitory effect on HIV replication in several human cell systems,

including natural peripheral blood lymphocytes (PBL) and freshly isolated monocyte/macrophages (M/M). The (R)-enantiomers of PMPDAP and PMPA were .apprx.10- to 100-fold more effective against HIV than their (S)-enantiomeric counterparts. The antiviral efficacy of (R)-PMPA was comparable to that of the prototype acyclic nucleoside phosphonate 9-(2-phosphonylmethoxyethyl)adenine (PMEA). The most potent and selective HIV inhibitor was (R)-PMPDAP. Its 50% effective concn. ranged from 0.01 .mu.M for HIV-1/Ba-L in M/M to 1-2.8 .mu.M for HIV-1/IIIB and HIV-1/HE in C8166, CEM, Molt/4, MT-4 and PBL cells. Both (R)-PMPA and (R)-PMPDAP were not toxic to the host cells at 300 .mu.M.

REFERENCE 8: 124:146698 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. II. The synthon approach. Holy, Antonin; Dvorakova, Hana; Masojidkova, Milena (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(8), 1390-409 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.

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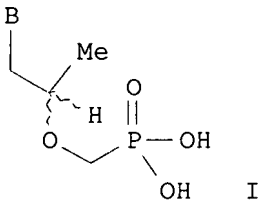
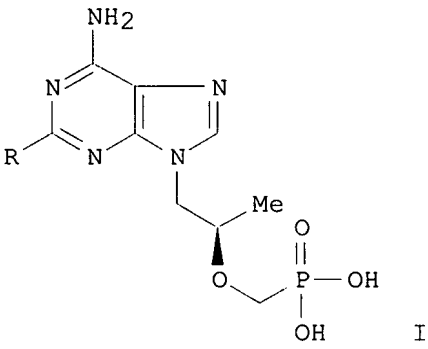


I

AB Acyclic nucleotides, e.g. I (B = adenine, guanine, hypoxanthine), were prepd. from the corresponding 1-benzyloxy-2-propanol.

REFERENCE 9: 124:117829 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. I. The stepwise approach. Holy, Antonin; Masojidkova, Milena (Inst. Org. Chem. Biochem., Acad. Sci., Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(7), 1196-212 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.

GI



I

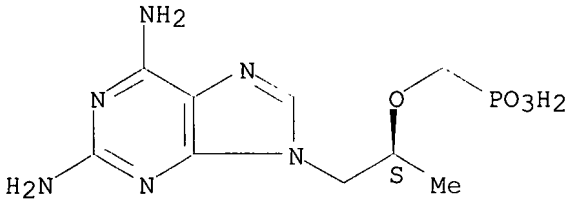
AB Phosphonomethoxypropyl acyclic nucleotide analogs, e.g. I (R = H, NH2), were prepd. via alkylation of N-protected N-(2-hydroxypropyl) derivs. of the corresponding bases with bis(2-propyl) p-toluenesulfonyloxymethylphosp honate. This approach was used for the synthesis of cytosine, adenine and 2,6-diaminopurine derivs., while compds. derived from guanine were prepd. by hydrolysis of 2-amino-6-chloropurine intermediates.

REFERENCE 10: 124:105675 Antiviral activity of selected acyclic nucleoside analogs against human herpes virus 6. Reymen, D.; Naesens, L.; Balzarini, J.; Holy, A.; Dvorakova, H.; De Clercq, E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Minderbroedersstraat 10, Louvain, B-3000, Belg.). Antiviral Res., 28(4), 343-57 (English) 1995. CODEN: ARSRDR. ISSN: 0166-3542.

AB Human herpes virus 6 (HHV-6) was examd. in vitro for its sensitivity to a broad range of nucleoside analogs, including acyclovir (ACV), ganciclovir (GCV), penciclovir (PCV), buciclovir (BCV), brivudin (BVDU), the N7-isomer of 6-deoxyganciclovir (S2242), foscarnet (phosphonoformic acid, PFA), and several acyclic nucleoside phosphonate (ANP) analogs such as (S)-HPMPA, (S)-HPMPC, PMEA and PMEDAP. Antiviral efficacy was monitored microscopically by the inhibitory effect of the compds. on HHV-6-induced cytopathic effect in human T-lymphoblastoid HSB-2 cells. In addn., a newly developed immunofluorescence/flow cytometric assay (FACS) was used to det. HHV-6-specific antigen expression. A close correlation was obsd. between the antiviral data obtained by the microscopic assay and the flow cytometric assay. Marked antiviral efficacy was noted for S2242, PFA and the ANP analogs (S)-HPMPA, (S)-HPMPC, (S)-cHPMPC, (S)-3-deaza-HPMPA, (S)-3-deaza-cHPMPA, (S)-HPMPG and (R)-HPMPG. Also, PMEA and PMEDAP proved highly active against HHV-6 infection, whereas (S)-FPMPA and (R)-PMPDAP were inactive. ACV was only slightly protective against HHV-6, and no activity was found for GCV, PCV, BCV and BVDU. Overall, the efficacy of the nucleoside analogs against HHV-6 appeared to correlate with their efficacy against human cytomegalovirus (HCMV).

L5 ANSWER 42 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 147057-09-8 REGISTRY
CN Phosphonic acid, [[(1S)-2-(2,6-diamino-9H-purin-9-yl)-1-methylethoxy]methyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[2-(2,6-diamino-9H-purin-9-yl)-1-methylethoxy]methyl]-, (S)-
OTHER NAMES:
CN (S)-9-(2-Phosphonomethoxypropyl)-2,6-diaminopurine
FS STEREOSEARCH
MF C9 H15 N6 O4 P
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



10 REFERENCES IN FILE CA (1967 TO DATE)
10 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:312634 Antiviral acyclic nucleoside phosphonate analogs as inhibitors of purine nucleoside phosphorylase. Kulikowska, E.; Bzowska, A.; Holy, A.; Magnowska, L.; Shugar, D. (Dep. Biophysics, Institute Experimental Physics, University Warsaw, Pol.). Adv. Exp. Med. Biol., 431(Purine and Pyrimidine Metabolism in Man IX, 1998), 747-752 (English) 1998. CODEN: AEMBAP. ISSN: 0065-2598. Publisher: Plenum Publishing Corp..

AB A new class of purine nucleoside phosphorylase (PNP) inhibitors comprises phosphonylalkoxyalkyl analogs of nucleotides which are broad-spectrum antiviral agents with potent and selective in vitro and in vivo activity vs. DNA viruses and retroviruses. It has been suggested that cellular PNP may play a role in the cytotoxic action of these compds.

REFERENCE 2: 129:130905 Inhibitory effects of novel nucleoside and nucleotide analogs on Epstein-Barr virus replication. Meerbach, A.; Holy, A.; Wutzler, P.; De Clercq, E.; Neyts, J. (Institute for Antiviral Chemotherapy, Friedrich-Schiller-University Jena, Erfurt, D-99089, Germany). Antiviral Chem. Chemother., 9(3), 275-282 (English) 1998. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.

AB The anti-Epstein-Barr virus (EBV) activity of different classes of compds. was assessed by means of an EBV DNA hybridization assay using a digoxigenin-labeled probe specific for the BamHI W fragment of the EBV genome, as well as by measuring viral capsid antigen (VCA) expression after a 7 day incubation period of P3HR-1 producer cells with the test substances. Several compds. proved to be potent and selective inhibitors of EBV DNA synthesis and VCA expression. Of the new compds. that were evaluated for their anti-EBV activity, the highest efficacy (lowest EC50) and highest selectivity index (SI) were shown by 2-amino-7-[(1,3-dihydroxy-2-propoxy)methyl]purine (S 2242) (EC50 0.6 ng/mL; SI 600), 9-[2-(phosphonomethoxy)ethyl]-6-(dimethylamino)purine (EC50 1.1 .mu.g/mL; SI 91), 9-[2-(phosphonomethoxy)ethyl]-2-amino-6-(benzhydrylamino)purine (EC50 1.3 .mu.g/mL; SI 29), 7-[2-(phosphonomethoxy)ethyl]-6-(dimethylamino)purine (EC50 0.8 .mu.g/mL; SI 56), 9-[(R)-2-(phosphonomethoxy)propyl]-6-[[2-(dimethylamino)ethyl]amino]purine (ECs50 0.5 .mu.g/mL; SI 42), 3'-oximino-2',3'-dideoxythymidine (EC50 1.5 g/mL; SI 65), and 1-[2,3-dideoxy-3-(hydroxyamino)-.beta.-D-threo-pentofuranosyl]thymine (EC50 4.1 .mu.g/mL; SI >24).

REFERENCE 3: 129:90065 Immunomodulatory properties of antiviral acyclic nucleotide analogs: cytokine stimulatory and nitric oxide costimulatory effects. Zidek, Zdenek; Holy, Antonin; Frankova, Daniela (Institute of Pharmacology, Academy of Sciences of the Czech Republic, Prague, 142 20/4,

Czech Rep.). Int. J. Immunopharmacol., Volume Date 1997, 19(9/10), 587-597 (English) 1998. CODEN: IJIMDS. ISSN: 0192-0561. Publisher: Elsevier Science Ltd..

AB Acyclic nucleotide analogs exhibit strong activity against a broad range of viruses, including HIV-1 and -2. Their effects on in vitro secretion of cytokines and prodn. of nitric oxide (NO) by murine peritoneal macrophages, factors known to play a role in virus replication, were investigated. Included in the study were the most prominent compds. of the series: 9-(2-phosphonomethoxyethyl)adenine, 9-(2-phosphonomethoxyethyl)-2,6-diaminopurine, (R)- and (S)-9-(2-phosphonomethoxypropyl)adenine [(R)- or (S)-PMPA], (R)- and (S)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine [(R)- or (S)-PMPDAP], 9-(2-phosphonomethoxyethyl)guanine (PMEG), and (S)-1-(3-hydroxy-2-phosphonomethoxypropyl)cytosine [(S)-HPMPC]. PMEG, (R)-PMPA, and (S)-PMPA greatly enhanced the secretion of both tumor necrosis factor-.alpha. (TNF-.alpha.) and interleukin-10 (IL-10), (R)-PMPDAP stimulated only TNF-.alpha., other test compds. were ineffective. None of them influenced the secretion of IL-2 or interferon-.gamma. (IFN-.gamma.). Both TNF-.alpha. and IL-10 have been found to be major factors detg. enhancing effects of PMEG, (R)-PMPA, and (S)-PMPA on prodn. of NO generated by exogenous IFN-.gamma.. The study points to a possible implication of immunomodulatory properties in the antiviral effects of some acyclic nucleotide analogs. In addn., the data support the view that endogenous IL-10 can stimulate certain macrophage functions.

REFERENCE 4: 126:31584 acyclic nucleosides as virucides and immunostimulation suppressants. Holy, Antonin; De Clercq, Erik Desire Alice (Ustav Organicke Chemie A Biochemie Akademie Ved C, Czech Rep.; De Clercq, Erik Desire Alice; Holy, Antonin; De Clercq, Erik, Desire, Alice).
PCT Int. Appl. WO 9633200 A1 19961024, 57 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-CZ11 19960419. PRIORITY: US 1995-426372 19950421.

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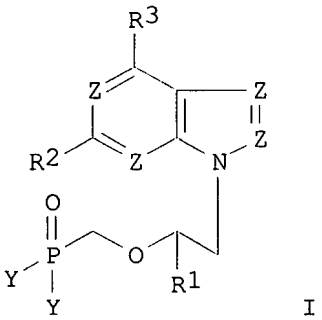

I

AB Acyclic nucleosides I [R1 = Me, C.tplbond.CH, CH:CH2, CH2F, azidomethyl; R2,R3 = H, NH2, alkylamine, alkoxyalkylamine; Y = OH, alkoxy, alkaryloxy, aryloxy, OPO3H2, OP2O6H2, aminoacid amidate, polypeptide amidate; Z = N, CH] were prepd. Thus, 6-amino-9-(R)-(2-phosphonomethoxypropyl)adenine was

tested as virucides and immunostimulation suppressants.

REFERENCE 5: 125:292255 Inhibition of murine lymphocyte proliferation by N6-substituted acyclic purine nucleoside phosphonates. Holy, Antonin; Zidek, Zdenek; Votruba, Ivan (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 61(Spec. Issue), S182-S187 (English) 1996. CODEN: CCCCAK. ISSN: 0010-0765.

AB Acyclic nucleoside phosphonate analogs substituted at the N6-position of the adenine and 2,6-diaminopurine ring exhibit remarkable inhibitory effects on mitogen-stimulated proliferation of murine spleen lymphocytes at concns. (IC50) starting from 10 nM. The effect depends on both phosphonomethoxyalkyl side chain and N6-substituents. Mitogen-stimulated T-cells were affected at much lower concns. than mitogen-stimulated B-cells.

REFERENCE 6: 124:249758 Activity of the (R)-enantiomers of 9-(2-phosphonylmethoxypropyl)-adenine and 9-(2-phosphonylmethoxypropyl)-2,6-diaminopurine against human immunodeficiency virus in different human cell systems. Balzarini, J.; Aquaro, S.; Perno, C.-F.; Witvrouw, M.; Holy, A.; De Clercq, E. (Rega Institute Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.). Biochem. Biophys. Res. Commun., 219(2), 337-41 (English) 1996. CODEN: BBRCA9. ISSN: 0006-291X.

AB The (S)- and (R)-enantiomers of 9-(2-phosphonylmethoxypropyl) derivs. of adenine (PMPA) and 2,6-diaminopurine (PMPDAP) were evaluated for their inhibitory effect on HIV replication in several human cell systems, including natural peripheral blood lymphocytes (PBL) and freshly isolated monocyte/macrophages (M/M). The (R)-enantiomers of PMPDAP and PMPA were .apprx.10- to 100-fold more effective against HIV than their (S)-enantiomeric counterparts. The antiviral efficacy of (R)-PMPA was comparable to that of the prototype acyclic nucleoside phosphonate 9-(2-phosphonylmethoxyethyl)adenine (PMEA). The most potent and selective HIV inhibitor was (R)-PMPDAP. Its 50% effective concn. ranged from 0.01 .mu.M for HIV-1/Ba-L in M/M to 1-2.8 .mu.M for HIV-1/IIIB and HIV-1/HE in C8166, CEM, Molt/4, MT-4 and PBL cells. Both (R)-PMPA and (R)-PMPDAP were not toxic to the host cells at 300 .mu.M.

REFERENCE 7: 124:146698 Synthesis of enantiomeric N-(2-phosphonomethoxypropyl) derivatives of purine and pyrimidine bases. II. The synthon approach. Holy, Antonin; Dvorakova, Hana; Masojidkova, Milena (Institute Organic Chemistry Biochemistry, Academy Sciences Czech Republic, Prague, 166 10, Czech Rep.). Collect. Czech. Chem. Commun., 60(8), 1390-409 (English) 1995. CODEN: CCCCAK. ISSN: 0010-0765.

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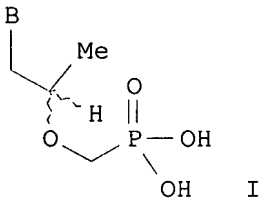
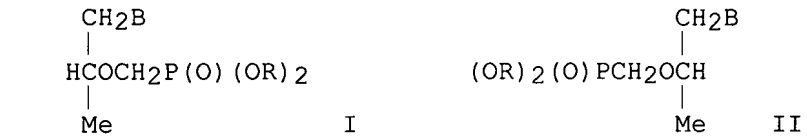


I

AB Acyclic nucleotides, e.g. I (B = adenine, guanine, hypoxanthine), were prepd. from the corresponding 1-benzyloxy-2-propanol.

REFERENCE 8: 122:106401 preparation of antiretroviral enantiomeric nucleotide analogs. Holy, Antonin; Dvorakova, Hana; Declercq, Erik Desire
Alice; Balzarini, Jan Marie Rene (Institute of Organic Chemistry and Biochemistry, Czech Rep.; Rega Stichting V.Z.W.; Gilead Sciences, Inc.). PCT Int. Appl. WO 9403467 A2 19940217, 96 pp. DESIGNATED STATES: W: CA, CZ, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US7360 19930804.
PRIORITY: US 1992-925610 19920805.
GI



AB Resolved enantiomers of formulas I and II [B is a purine or pyrimidine base; R = H, C1-6 alkyl, aryl, aralkyl] or their aza and/or deaza analogs,
useful in antiviral pharmaceutical compns. to treat retroviral infections,
are prepd. via hydrolysis of the appropriate phosphate ester. E.g., iso-Bu (R)-lactate was protected with 3,4-dihydro-2H-pyran, the resulting iso-Bu (R)-2-O-(tetrahydropyranyl)lactate was reduced with LiAlH4, the resulting 2-O-(tetrahydropyranyl)-(R)-propane-1,2-diol was 1-O-tosylated, the resulting 1-O-tosyl-2-O-(tetrahydropyranyl)propane-1,2-diol was reacted with adenine in DMF contg. cesium carbonate and the product was deprotected, the resulting 9-(R)-(2-hydroxypropyl)adenine was first N6-benzoylated and the product was treated with diisopropyl (p-toluenesulfonyloxy)methylphosphonate in DMF contg. NaH, the product was
deprotected at the N6 position with MeONa-MeOH followed by hydrolysis to give (2'R)-I [B = 9-adeninyl, R = isopropyl]. In an in vitro study this had an EC50 of 1.7 and 1.4 .mu.g/Ml, resp., against HIV-1- and HIV-2-induced cytopathicity in human lymphocyte MT-4 cells.

REFERENCE 9: 120:94856 Inhibition of visna virus replication by 2',3'-dideoxynucleosides and acyclic nucleoside phosphonate analogs. Thormar, Hallidor; Balzarini, Jan; Holy, Antonin; Jindrich, Jindrich; Rosenberg, Ivan; Debyser, Zeger; Desmyter, Jan; De Clercq, Erik (Inst. Biol., Univ. Iceland, Reykjavik, 108, Iceland). Antimicrob. Agents Chemother., 37(12), 2540-4 (English) 1993. CODEN: AMACCQ. ISSN: 0066-4804.
AB A series of acyclic nucleoside phosphonate (ANP) and 2',3'-dideoxynucleoside (ddN) derivs. were evaluated for their inhibitory effects on visna virus replication and maedi/visna virus-induced syncytium
formation in sheep choroid plexus cells. Most ANP derivs. inhibited virus
replication and syncytium formation within a concn. range of 0.2 to 1.8 .mu.M. Among the most active ANP derivs. ranked (R)-9-(2-phosphonomethoxypropyl)adenine, (R)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine, and (S)-9-(3-fluoro-2-phosphonomethoxypropyl)adenine. Of the ddN derivs., 2',3'-dideoxycytidine (ddCyd) proved to be the most inhibitory to visna virus-induced syncytium formation (50% effective

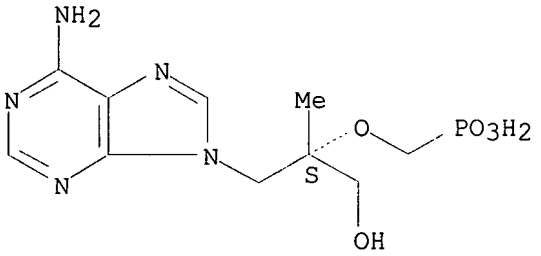
concn., 0.02 .mu.M). The purine ddN analogs (i.e., 2',3'-dideoxyinosine, 2',3'-dideoxyadenosine, 2',3'-dideoxyguanosine, and 2,6-diaminopurine-2',3'-dideoxyribosine) were 10- to 30-fold less effective, and the thymidine derivs. 2',3'-didehydro-2',3'-dideoxythymidine (D4T) and 3'-azido-2',3'-dideoxythymidine (AZT) were more than 500-fold less inhibitory to visna virus than ddCyd. The 5'-triphosphate forms of AZT and D4T were 100- to 600-fold more inhibitory to visna virus particle-derived reverse transcriptase than was the 5'-triphosphate of ddCyd. The apparent discrepancy between the inhibitory effects of these ddN derivs. on virus replication and viral reverse transcriptase activity most likely reflects differences in the metabolic conversion of ddCyd vs. D4T and AZT in sheep choroid plexus cells.

REFERENCE 10: 118:182782 Differential anti-herpes virus and anti-retrovirus effects of the (S) and (R) enantiomers of acyclic nucleoside phosphonates:
potent and selective in vitro and in vivo antiretrovirus activities of (R)-9-(2-phosphonomethoxypropyl)-2,6-diaminopurine. Balzarini, J.; Holy, A.; Jindrich, J.; Naesens, L.; Snoeck, R.; Schols, D.; De Clercq, E. (Rega
Inst. Med. Res., Kathol. Univ. Leuven, Louvain, B-3000, Belg.). Antimicrob. Agents Chemother., 37(2), 332-8 (English) 1993. CODEN: AMACCQ. ISSN: 0066-4804.

AB The (S)- and (R)-enantiomers of acyclic purine nucleoside phosphonate analogs [i.e., 3-hydroxy-2-phosphonomethoxypropyl (HPMP) derivs., 3-fluoro-2-phosphonomethoxypropyl (FPMP) derivs., and 2-phosphonomethoxypropyl (PMP) derivs. of adenine (A), 2-aminopurine, 2,6-diaminopurine (DAP), and guanine (G)] were synthesized and evaluated for antiviral activity. Athe HPMP derivs. were effective against DNA viruses but not RNA viruses or retroviruses. In particular, (S)-HPMPA, (S)-HPMPDAP, and (R)- and (S)-HPMPG were exclusively inhibitory to herpes simplex virus type 1 (50% effective concns., 0.63, 0.22, 0.10, and 0.66 .mu.M, resp.). The FPMP and PMP derivs. showed marked inhibitory activities against retroviruses but not DNA viruses. The (S)-enantiomer of FPMPA and the (R)-enantiomer of PMPA were .apprx.30- to 100-fold more effective against human immunodeficiency virus and Moloney murine sarcoma virus (MSV) than their enantiomeric counterparts. In contrast, both (S)- and (R)-enantiomers of the DAP and G derivs. were equally effective against retroviruses, except for (R)-PMPDAP, which was 15- to 40-fold more
inhibitory than (S)-PMPDAP. (R)-PMPDAP emerged as the most potent and selective inhibitor of MSV-induced transformation of murine C3H/3T3 cells and human immunodeficiency virus-induced cytotoxicity in MT-4 and CEM cells (50% effective concn., .apprx.0.1 to 0.6 .mu.M). When administered i.p. in a single dose as low as 2 mg/kg, (R)-PMPDAP efficiently decreased MSV-induced tumor formation in newborn NMRI mice and significantly increased the survival time of MSV-infected mice. In addn., upon oral administration of MSV-infected mice, (R)-PMPDAP showed marked antiretroviral efficacy.

L5 ANSWER 43 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 123156-57-0 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-(hydroxymethyl)-1-methylethoxy]methyl]-, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C10 H16 N5 O5 P
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 111:174565 Acyclic nucleotide analogs. IV. Phosphonylmethoxyalkyl and phosphonylalkyl derivatives of adenine. Rosenberg, Ivan; Holy, Antonin; Masojidkova, Milena (Inst. Org. Chem. Biochem., Czech. Acad. Sci., Prague, 166 10, Czech.). Collect. Czech. Chem. Commun., 53(11B), 2753-77 (English) 1988. CODEN: CCCCAK. ISSN: 0010-0765.

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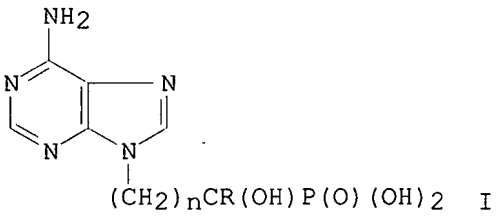
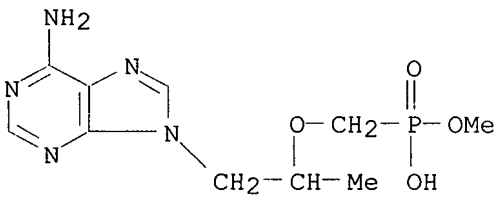


AB The prepn. of a variety title compds. including I (n = 1, 2; R = H, Me) from adenine and adenine derivs. is reported.

L5 ANSWER 44 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 123155-85-1 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, monomethyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]-, monomethyl ester, (.+-.)-
FS 3D CONCORD
MF C10 H16 N5 O4 P
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT
(*File contains numerically searchable property data)



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 111:174565 Acyclic nucleotide analogs. IV. Phosphonylmethoxyalkyl and phosphonylalkyl derivatives of adenine. Rosenberg, Ivan; Holy, Antonin; Masojidkova, Milena (Inst. Org. Chem. Biochem., Czech. Acad. Sci., Prague, 166 10, Czech.). Collect. Czech. Chem. Commun., 53(11B), 2753-77 (English) 1988. CODEN: CCCCAK. ISSN: 0010-0765.

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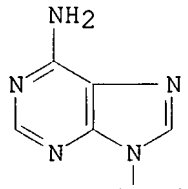

$(CH_2)_nCR(OH)P(O)(OH)_2$ I

AB The prepn. of a variety title compds. including I (n = 1, 2; R = H, Me) from adenine and adenine derivs. is reported.

L5 ANSWER 45 OF 45 REGISTRY COPYRIGHT 1999 ACS
RN 107021-12-5 REGISTRY
CN Phosphonic acid, [[2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]- (9CI)
(CA INDEX NAME)
FS 3D CONCORD
DR 121149-89-1
MF C9 H14 N5 O4 P
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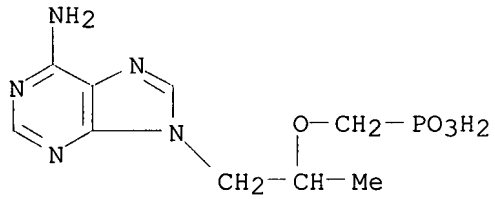
LC STN Files: AIDSLINE, BEILSTEIN*, CA, CANCERLIT, CAPLUS, CASREACT, MEDLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)



4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 129:58771 Composition and method for storing nucleotide analogs. Yuan, Lung-chi J. (Gilead Sciences, Inc., USA). U.S. US 5763424
A 19980609, 11 pp. (English). CODEN: USXXAM. APPLICATION: US 1996-622721 19960326.

AB The invention provides compns. and methods to prevent the appearance of visually detectable ppt. in the compn. upon storage of an aq. soln. of the compn. contg. 5-250 mg/mL of the phosphonate nucleotide analog for at

least 6 mo at 22.degree. where the compn. comprises a phosphonate nucleotide analog and a sufficient amt. of a divalent or trivalent metal cation sequestering agent such as about 0.1% w/v EDTA, and/or a sufficiently low concn. of a divalent or trivalent metal cation, e.g., about 3-10 ppm, and/or a sufficient pH in water, e.g., a pH of about 7.0-7.5.

REFERENCE 2: 126:220323 A zidovudine-resistant simian immunodeficiency virus
mutant with a Q151M mutation in reverse transcriptase causes AIDS in newborn macaques. Van Rompay, Koen K. A.; Greenier, Jennifer L.; Marthas, Marta L.; Otsyula, Moses G.; Tarara, Ross P.; Miller, Christopher J.; Pedersen, Niels C. (California Regional Primate Res. Cent., Univ. California, Davis, CA, 95616, USA). Antimicrob. Agents Chemother., 41(2), 278-283 (English) 1997. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.

AB The simian immunodeficiency virus (SIV)-newborn rhesus macaque model of AIDS can be used to study directly the virulence of viral mutants which are resistant to antiviral drugs. A viral mutant called SIVmac79A6.1, isolated from an SIV-infected macaque after prolonged zidovudine treatment, was found to have a double-base-pair change at codon 151 of reverse transcriptase, resulting in a glutamine to methionine substitution (Q151M). This mutation was assocd. with more than 100-fold increased resistance to zidovudine and low-level cross-resistance to other dideoxynucleoside analogs. To det. whether this Q151M mutation affects viral virulence, four newborn macaques were inoculated i.v. with a biol. clone of this drug-resistant SIVmac79A6.1 mutant; two of these animals were also treated orally with zidovudine. All four animals shoed persistent viremia, and two of the four animals developed fatal immunodeficiency at 3 and 8 mo of age, resp. The remaining two animals had CD4+ T-cell depletion and clin. symptoms of AIDS at 22 mo. No phenotypic or genotypic reversion of virus to the wild type could be detected in any of the four animals. These results demonstrate that the Q151M mutation in SIV reverse transcriptase does not reduce viral virulence.

REFERENCE 3: 120:170 Metabolism and in vitro antiretroviral activities of bis(pivaloyloxymethyl) prodrugs of acyclic nucleoside phosphonates. Srinivas, R. V.; Robbins, B. L.; Connelly, M. C.; Gong, Y. F.; Bischofberger, N.; Fridland, A. (Dep. Infect. Dis., St. Jude Child. Res. Hosp., Memphis, TN, 38101, USA). Antimicrob. Agents Chemother., 37(10), 2247-50 (English) 1993. CODEN: AMACCQ. ISSN: 0066-4804.

AB Bis(pivaloyloxymethyl) [bis(pom)] esters of the acyclic nucleoside phosphonates 9-(2-phosphonylmethoxyethyl)adenine (PMEA), 9-(2-phosphonylmethoxypropyl)adenine, and 9-(2-phosphonylmethoxypropyl)diaminopurine exhibited 9-23-fold greater antiviral activity (against HIV-1) than their corresponding unmodified compds. The cytotoxicity of the bis(pom) analogs to the host MT-2 cells was also increased by various degrees, thus altering the therapeutic indexes of these compds. Metabolic studies using [3H]bis(pom)PMEA and [3H]PMEA as model compds. suggested a >100-fold increase in the cellular uptake of the bis(pom) deriv. and formation of active diphosphorylated metabolite. However, the bis(pom) derivs. were chem. unstable and highly susceptible to serum-mediated hydrolysis, factors which limit their potential utility for intracellular drug delivery.

REFERENCE 4: 106:214308 Preparation of 9-[(phosphonomethoxy)alkyl]adenines and their use as virucides. Holy, Antonin; Rosenberg, Ivan

(Ceskoslovenska Akademie Ved , Czech.). Eur. Pat. Appl. EP 206459 A2 19861230, 25 pp. DESIGNATED STATES: R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE. (English). CODEN: EPXXDW. APPLICATION: EP 1986-302822 19860416. PRIORITY: CS 1985-3017 19850425.

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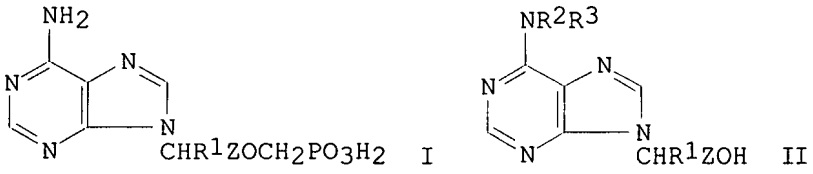

AB Title compds. [I; R1 = H, C1-3 alkyl, HOCH2; Z = (un)substituted alkylene]
and their salts, useful against Moloney sarcoma (no data) and as virucides, were prepd. by treating (hydroxyalkyl)adenines II (R2 = Bz; R3 = H, Bz; R2R3 = Me2NCH) with 4-MeC6H4SO3CH2P(O)(OR4)2 (III; R4 = Me, Et). II (R1 = R3 = H, R2 = Bz; Z = CH2) in DMF was treated with NaH and III (R4
= Me) and the product deesterified by treatment with Me3SiI and Et3N.H2CO3
to give I (R1 = H, Z = CH2) (IV). In rabbit kidney cells infected for 1 h
with HSV-1 and incubated for 48 h with 100 .mu.g IV/mL, the virus titer decreased by a factor of 14,500. At 7 .mu.g/mL IV showed a 50% inhibition
of the cytopathic effect of HSV-2 in rabbit kidney cells infected at a dose 100 times larger than that necessary to induce 50% of the cytopathic effect of the virus.

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L10 0 FILE WPIDS

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L21 1 FILE EMBASE
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TOTAL FOR ALL FILES
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PROCESSING COMPLETED FOR L23
L24 5 DUP REM L23 (3 DUPLICATES REMOVED)

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L24 ANSWER 1 OF 5 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 1999-153293 [13] WPIDS
AB WO 9904774 A UPAB: 19990331
Composition comprises crystalline adefovir dipivoxil (AD) ([[bis[(pivaloyloxy)-methoxy]phosphinyl]methoxy]ethyl]adenine). Also claimed are (A) a method comprising contacting a crystallisation solvent and AD; (B) preparation of Form 2 AD which comprises forming the crystals in the presence of water; (C) a method comprising contacting AD with methanol; (D) preparation of Form 4 AD which comprises forming crystals in
the presence of fumaric acid; (E) preparation of AD which comprises contacting 9-[2-(**phosphonomethoxy**)ethyl]adenine, particularly containing < 2% salt with chloromethyl pivalate in 1-methyl-2-pyrrolidinone and a trialkylamine and recovering AD; (F) a product produced by compression of AD with an excipient or by preparing wet granules from a mixture of a liquid, Form 1 AD and an excipient; (G) a

composition comprising a tablet containing AD, pregelatinised starch (20 mg), croscarmellose sodium lactose monohydrate (24 mg), talc (24 mg), and magnesium stearate (4 mg), in which AD comprises at least 70% Form 1 AD and (H) the preparation of 9-[2-(**phosphonomethoxy**)ethyl]adenine which comprises contacting sodium alkoxide and 9-(2-hydroxyethyl)-adenine.

USE - Adefovir dipivoxil has **antiviral** activity.

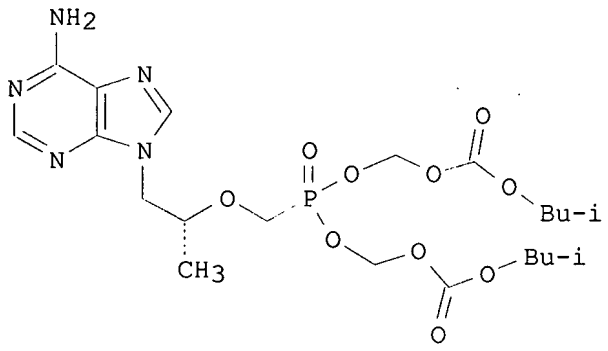
ADVANTAGE - The crystalline forms of AD have desirable melting point and flow or bulk density properties, suitable for large scale manufacture, can be purified to > 98% and are storage-stable.

Dwg.0/29

L24 ANSWER 2 OF 5 CAPLUS COPYRIGHT 1999 ACS

1998:102883 Document No. 128:140970 Preparation of **phosphonomethoxy** acyclic nucleotide analogs as **antiviral** agents. **Arimilli, Murty N.**; Cundy, Kenneth C.; Dougherty, Joseph P.; Kim, Choung U.; Oliyai, Reza; Stella, Valentino J. (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9804569 A1 19980205, 74 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US13244 19970725. PRIORITY: US 1996-686838 19960726; US 1996-22708 19960726.

GI



I

AB Compds. are provided that comprise esters of **antiviral** **phosphonomethoxy** nucleotide analogs with carbonates and/or carbamates having the structure B-OC(R2)2OC(O)X(R)n, wherein R2 independently is H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro or OR3 in which R3 is C1-C12 alkyl; X is N or O; R is independently H, C1-C12 alkyl, aryl, alkenyl, alkynyl, alkyenylaryl, alkynylaryl, alkaryl, arylalkynyl, arylalkenyl or arylalkyl which is (un)substituted with halo, azido, nitro, -O-, -N=, -NR4, -N(R4)2- or OR3, R4 independently is -H or C1-C8 alkyl, provided that at least one R is not H; and n is 1 or 2, with the proviso that when n is 2 and X is N, (a) two R groups can be taken together to form a carbocycle or oxygen-contg. heterocycle, or (b) one R addnl. can be OR3. The compds. are useful as intermediates for the prepn. of **antiviral** compds. or oligonucleotides, or are useful for

administration directly to patients for **antiviral** therapy or prophylaxis. Embodiments are particularly useful when administered orally. Thus , acyclic nucleotide I was prepd. and showed anti-HIV activity (IC50 < 0.001 .mu.M).

L24 ANSWER 3 OF 5 MEDLINE
1998325414 Document Number: 98325414. Antiretroviral efficacy and pharmacokinetics of oral bis(isopropyloxycarbonyloxymethyl)-9-(2-phosphonylmethoxypropyl)adenine in mice. Naesens L; Bischofberger N; Augustijns P; Annaert P; Van den Mooter G; **Arimilli M N**; Kim C U; De Clercq E. (Rega Institute for Medical Research, Leuven, Belgium.. lieve.naesens@rega.kuleuven.ac.be). ANTIMICROBIAL AGENTS AND CHEMOTHERAPY,
(1998 Jul) 42 (7) 1568-73. Journal code: 6HK. ISSN: 0066-4804. Pub. country: United States. Language: English.
AB To overcome the low oral bioavailability of the highly potent and selective antiretroviral agent (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), a new lipophilic ester derivative, i.e., the bis(isopropyloxycarbonyloxymethyl)-ester [bis(POC)-PMPA], was prepared. The usefulness of bis(POC)-PMPA as an oral prodrug for PMPA was investigated in the intestinal mucosa Caco-2 cell monolayer model. The total transport of bis(POC)-PMPA was 2.7%, whereas it was less than 0.1% for PMPA. Bis(POC)-PMPA was considerably metabolized inside the epithelial cells, since the majority of the compound was recovered after transport in the form of the monoester metabolite [mono(POC)-PMPA]. In contrast, bis(POC)-PMPA was relatively resistant to degradation at the luminal side of the Caco-2 cells. Pharmacokinetic studies with mice showed that the oral bioavailability of bis(POC)-PMPA (calculated from the curves of the concentration of free PMPA in plasma) was 20%. Neither bis(POC)-PMPA nor mono(POC)-PMPA could be recovered in plasma, suggesting the efficient release of the active drug PMPA after oral administration of bis(POC)-PMPA. Severe combined immunodeficient (SCID) mice infected with Moloney murine sarcoma virus (MSV) and treated orally with bis(POC)-PMPA for 5 or 10 days (dosages, 50, 100, or 200 mg of PMPA equivalent per kg of body weight per day) showed a significant delay in MSV-induced tumor appearance and tumor-associated death. The **antiviral** efficacy of oral bis(POC)-PMPA was related to the dosage and treatment period and was not significantly different from that of subcutaneous PMPA given at an equivalent dose. The favorable pharmacokinetic profile, marked **antiviral** efficacy, and low toxicity make bis(POC)-PMPA an attractive oral prodrug of PMPA that should be further pursued in clinical studies with patients infected with human immunodeficiency virus or hepatitis B virus.

L24 ANSWER 4 OF 5 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 1
1997:762860 Document No. 128:97300 Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(**phosphonomethoxy**)propyl]adenine (PMPA) prodrugs. **Arimilli, M. N.**; Kim, C. U.; Dougherty, J.; Mulato, A.; Oliyai, R.; Shaw, J. P.; Cundy, K. C.; Bischofberger, N. (Gilead Sci., Foster City, CA, 94404, USA). Antiviral Chem. Chemother., 8(6), 557-564 (English) 1997. CODEN: ACCHEH. ISSN: 0956-3202. Publisher: International Medical Press.
AB Potentially orally bioavailable prodrugs of the antiretroviral agent 9-[2-(**phosphonomethoxy**)propyl]adenine (PMPA) were evaluated. Alkyl Me carbamates were synthesized by alkylation of PMPA with the corresponding alkyl chloromethyl carbonate and N-alkyl chloromethyl

carbamate reagents. The prodrugs were evaluated for in vitro **antiviral** activity in addn. to chem. and enzymic stability. The inhibition of human immunodeficiency virus type 1 (HIV-1) strain IIIB replication of MT-2 cells by the carbonate prodrugs was found to be 2.5-500-fold increased compared to PMPA. The alkyl Me carbonates, except t-Bu Me carbonate, had reasonable chem. stability at pH 2.2 and 7.4, but were rapidly converted to the corresponding monoester of PMPA in the presence of dog plasma. The alkyl Me carbamate prodrugs such a N-t-Bu Me carbamate were found to have high stability in vitro. Based on its chem. stability and good oral bioavailability, bis(POC)PMPA (iso-Pr methylcarbonate) was chosen as a clin. candidate.

L24 ANSWER 5 OF 5 MEDLINE DUPLICATE 2
97227272 Document Number: 97227272. Pharmacokinetics and metabolism of selected prodrugs of PMEA in rats. Shaw J P; Louie M S; Krishnamurthy V V;
Arimilli M N; Jones R J; Bidgood A M; Lee W A; Cundy K C. (Gilead Sciences, Inc., Foster City, CA 94404, USA.)DRUG METABOLISM AND DISPOSITION, (1997 Mar) 25 (3) 362-6. Journal code: EBR. ISSN: 0090-9556.
Pub. country: United States. Language: English.
AB The oral bioavailability of PMEA [9-[2-(**phosphonomethoxy**)ethyl]adenine; adefovir) has been determined in rats from three bisester prodrugs of PMEA: bis-(pivaloyloxymethyl) PMEA (bis-POM PMEA), bis-(phenyl) PMEA, and bis-(o-ethoxyphenyl) PMEA. The prodrugs were each administered to 9 male rats as solutions in PEG 400 at a dose of 10 mg-equivalent of PMEA per kg. Plasma samples were obtained over the course of 12 hr and concentrations of PMEA were determined by fluorescence derivatization and analysis by HPLC. Concentrations of PMEA observed in plasma following oral administration of PMEA prodrugs were compared with levels observed for intravenous PMEA. The observed oral bioavailabilities of PMEA from bis-POM PMEA, bis-(phenyl) PMEA, and bis-(o-ethoxyphenyl) PMEA were 38.2%, 2.46%, and 40.1%, respectively. PMEA was the only metabolite formed after oral administration of bis-POM PMEA. Three metabolites were detected after oral administration of either bis-(phenyl) PMEA or bis-(o-ethoxyphenyl) PMEA to rats: PMEA, the corresponding monoester, and 2-adenylacetic acid. The major metabolite of bis-(phenyl) PMEA was 2-adenylacetic acid following oral administration. 2-Adenylacetic acid appears to have been formed from the intact prodrugs by a P450 mediated oxidation of the ethyl side chain.

L25 3 FILE MEDLINE
L26 4 FILE CAPLUS
L27 5 FILE BIOSIS
L28 4 FILE EMBASE
L29 1 FILE WPIDS

TOTAL FOR ALL FILES
L30 17 L17 AND ORAL BIOAVAIL?

=> s l30 not l23

L31 1 FILE MEDLINE
L32 3 FILE CAPLUS
L33 3 FILE BIOSIS
L34 3 FILE EMBASE
L35 1 FILE WPIDS

TOTAL FOR ALL FILES
L36 11 L30 NOT L23

=> dup rem l36

PROCESSING COMPLETED FOR L36
L37 5 DUP REM L36 (6 DUPLICATES REMOVED)

=> d cbib abs 1-5

L37 ANSWER 1 OF 5 CAPLUS COPYRIGHT 1999 ACS DUPLICATE 1
1998:436276 Document No. 129:170075 Antiretroviral efficacy and pharmacokinetics of oral bis(isopropyloxycarbonyloxymethyl)-9-(2-phosphonylmethoxypropyl)adenine in mice. Naesens, Lieve; Bischofberger, Norbert; Augustijns, Patrick; Annaert, Pieter; Van Den Mooter, Guy; **Arimilli, Murty N.**; Kim, Choung U.; De Clercq, Erik (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.). Antimicrob. Agents Chemother., 42(7), 1568-1673 (English)
1998. CODEN: AMACCQ. ISSN: 0066-4804. Publisher: American Society for Microbiology.
AB To overcome the low **oral bioavailability** of the highly potent and selective antiretroviral agent (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), its lipophilic ester deriv. bis(isopropyloxycarbonyloxymethyl)-ester [bis(POC)-PMPA] was prepd. The usefulness of bis(POC)-PMPA as an oral prodrug for PMPA was investigated in the intestinal mucosa Caco-2 cell monolayer model. The total transport of bis(POC)-PMPA was 2.7%, whereas it was <0.1% for PMPA. Bis(POC)-PMPA was considerably metabolized inside the epithelial cells, since the majority of the compd. was recovered after transport in the form of the monoester metabolite mono(POC)-PMPA. Bis(POC)-PMPA was relatively resistant to degrdn. at the luminal side of the Caco-2 cells. Pharmacokinetic studies in mice showed that the **oral bioavailability** of bis(POC)-PMPA calcd. from the curves of the concn. of free PMPA in blood plasma was 20%. Neither bis(POC)-PMPA nor mono(POC)-PMPA could be recovered from blood plasma, suggesting the efficient release of the active drug PMPA after oral administration of bis(POC)-PMPA. Severe combined immunodeficient (SCID) mice infected with Moloney murine sarcoma virus (MSV) and treated orally with bis(POC)-PMPA for 5 or 10 days at dosages of 50, 100, or 200 mg PMPA equiv./kg/day showed a significant delay in MSV-induced tumor appearance and tumor-assocd. death. The antiviral efficacy of oral bis(POC)-PMPA was related to the dosage and treatment period and was not significantly different from that of s.c. PMPA given at equiv. doses. The favorable pharmacokinetic profile, marked antiviral efficacy, and low toxicity make bis(POC)-PMPA an attractive oral prodrug of PMPA that should be pursued in clin. studies in patients infected with human immunodeficiency virus or hepatitis B virus.

L37 ANSWER 2 OF 5 WPIDS COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 1997-372483 [34] WPIDS
CR 1995-139317 [18]; 1995-139318 [18]
AB WO 9724361 A UPAB: 19990518
Nucleotide analogues of formula (I), their racemates, salts and solvates are new; B = optionally protected heterocyclic base; R = H, alkyl, alkoxy, CHO, CH2CH2C6H5, COOR2, COR2, CON(R3)2 or SOON(R3)2; R1 = H, CN, NO2,

halo, alkyl, alkoxy, COOR3, COR3, SOOOH, N(R3)2, CHO or OH; R2, R3 = H, alkyl, phenyl, alkyl substituted phenyl, CH2C6H5 or CH2CH2C6H5; provided that compounds where the ring containing R and R1 comprises phenyl (optionally substituted by 1-4 halo, 1 or 2 CN, NO2, OH, 1-12C alkyl or 1-12C alkoxy, 2 COOC2H5, 1 N(Me)2 or COO-1-4C alkyl or 1 COOC2H5 or OC2H5 and 1 OH are excluded.

USE - (I) have antiviral activity when administered orally (claimed).

They can be used against viruses malignant cells and/or parasitic protozoa, e.g. herpes viruses (e.g. herpes simplex virus, human cytomegalovirus, pseudorabies virus and vaccinia), African swine fever, Japanese encephalitis viruses, togaviruses, influenza viruses, retroviruses (e.g. human immunodeficiency virus), adenoviruses, poxviruses, enteroviruses, gastroenteritis viruses, hantaviruses, papovaviruses, rhinoviruses, parainfluenza virus types 1-4 and rabies virus. They may also be used in tissue culture systems to eliminate or reduce viral spread or growth during the production of biopharmaceuticals or other products such as proteins or vaccines, to eliminate or reduce viral spread or growth in clinical samples such as blood and to reduce or block growth of viruses in tissue culture without interfering with protein production. (I) can be used to treat parasitic protozoan infections, e.g. Histomonas, Pneumocystis, Trypanosoma, Giardia, Plasmodium, Trypanosoma cruzi and Trichomonas vaginalis. They can also be used to treat yeast or fungal infections caused by e.g. Candida sp., Cryptococcus sp., Blastomyces sp., Torulopsis sp., Coccidioides sp. and Aspergillus sp. and also for treatment of acquired immunodeficiency syndrome, multiple sclerosis and topical spastic paraparesis.

ADVANTAGE - (I) have improved pharmacokinetic or pharmacodynamic properties compared to the parent nucleotide analogue that lacks the ester moiety. They usually have increased **oral bioavailability** in humans and animals and also have reduced toxicity and/or increased potency and increase the therapeutic window for the parent compound as they are supplied in a form that is less toxic in vivo, while retaining the parent antiviral activity. (I) also deesterify while permitting subsequent biochemical or enzymatic conversion of the cyclic nucleotide analogue to a desired ring opened derivative.

Dwg.0/0

ABEQ US 5717095 A UPAB: 19980330

Nucleotide analogues of formula (I), their racemates, salts and solvates are new; B = optionally protected heterocyclic base; R = H, alkyl, alkoxy, CHO, CH2CH2C6H5, COOR2, COR2, CON(R3)2 or SOON(R3)2; R1 = H, CN, NO2, halo, alkyl, alkoxy, COOR3, COR3, SOOOH, N(R3)2, CHO or OH; R2, R3 = H, alkyl, phenyl, alkyl substituted phenyl, CH2C6H5 or CH2CH2C6H5; provided that compounds where the ring containing R and R1 comprises phenyl (optionally substituted by 1-4 halo, 1 or 2 CN, NO2, OH, 1-12C alkyl or 1-12C alkoxy, 2 COOC2H5, 1 N(Me)2 or COO-1-4C alkyl or 1 COOC2H5 or OC2H5 and 1 OH are excluded.

USE - (I) have antiviral activity when administered orally (claimed).

They can be used against viruses malignant cells and/or parasitic protozoa, e.g. herpes viruses (e.g. herpes simplex virus, human cytomegalovirus, pseudorabies virus and vaccinia), African swine fever, Japanese encephalitis viruses, togaviruses, influenza viruses, retroviruses (e.g. human immunodeficiency virus), adenoviruses, poxviruses, enteroviruses, gastroenteritis viruses, hantaviruses, papovaviruses, rhinoviruses, parainfluenza virus types 1-4 and rabies virus. They may also be used in tissue culture systems to eliminate or reduce viral spread or growth during the production of biopharmaceuticals

or other products such as proteins or vaccines, to eliminate or reduce viral spread or growth in clinical samples such as blood and to reduce or block growth of viruses in tissue culture without interfering with protein production. (I) can be used to treat parasitic protozoan infections, e.g. Histomonas, Pneumocystis, Trypanosoma, Giardia, Plasmodium, Trypanosoma cruzi and Trichomonas vaginalis. They can also be used to treat yeast or fungal infections caused by e.g. Candida sp., Cryptococcus sp., Blastomyces sp., Torulopsis sp., Coccidioides sp. and Aspergillus sp. and also for treatment of acquired immunodeficiency syndrome, multiple sclerosis and topical spastic paraparesis.

ADVANTAGE - (I) have improved pharmacokinetic or pharmacodynamic properties compared to the parent nucleotide analogue that lacks the ester moiety. They usually have increased **oral bioavailability** in humans and animals and also have reduced toxicity and/or increased potency and increase the therapeutic window for the parent compound as they are supplied in a form that is less toxic in vivo, while retaining the parent antiviral activity. (I) also deesterify while permitting subsequent biochemical or enzymatic conversion of the cyclic nucleotide analogue to a desired ring opened derivative.

Dwg.0/0

L37 ANSWER 3 OF 5 MEDLINE DUPLICATE 2

1998115165 Document Number: 98115165. Metabolism and pharmacokinetics of novel oral prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in dogs. Shaw J P; Sueoko C M; Oliyai R; Lee W A; **Arimilli M N**; Kim C U; Cundy K C. (Gilead Sciences, Inc., Foster City, California 94404, USA.)PHARMACEUTICAL RESEARCH, (1997 Dec) 14 (12) 1824-9. Journal code: PHS. ISSN: 0724-8741. Pub. country: United States. Language: English.

AB PURPOSE: A series of prodrugs designed to enhance the **oral bioavailability** of the antiretroviral agent 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA; 1) have been synthesized, including a bis-(acyloxymethyl) ester 2 and a series of bis-(alkoxycarbonyloxymethyl) esters 3-9. The in vitro biological stability and in vivo pharmacokinetics of these prodrugs were evaluated to support selection of a prodrug candidate for clinical evaluation. METHODS: The in vitro biological stability of the prodrugs was examined in dog tissues (intestinal homogenate, plasma and liver homogenate). The apparent half-lives were determined based on the disappearance of prodrug using reverse-phase HPLC with UV detection. **Oral bioavailability** of PMPA from each prodrug was determined in fasted beagle dogs. Concentrations of PMPA in plasma were determined by HPLC following fluorescence derivatization. Data for prodrugs were compared to historical data for intravenous PMPA. RESULTS: All prodrug were rapidly hydrolyzed in dog plasma and tissues (t1/2 < 60 min). In fasted beagle dogs, bis-[(pivaloyloxy)methyl] PMPA (bis-POM PMPA) 2 had the highest **oral bioavailability** as PMPA (37.8 +/- 5.1%). The **oral bioavailabilities** of PMPA from bis-(alkoxycarbonyloxymethyl) esters ranged from 16.0% to 30.7% and PMPA was the major metabolite formed. CONCLUSIONS: There was a correlation between **oral bioavailability** and intestinal stability of bis-(alkoxycarbonyloxymethyl) ester prodrugs (r2 = 0.96). Lipophilicity (log P) was not a good predictor of **oral bioavailability**. The most labile prodrugs in dog intestinal homogenates, bis-(n-butyloxycarbonyloxymethyl) PMPA 5 and bis-(neo-pentyloxy-carbonyloxymethyl) PMPA 8 (t1/2 < 5 min) had the lowest **oral**